Food Safety
AUTHORITY OF IRELAND

Report of the Scientific Committee
of the Food Safety Authority of Ireland

2015

Potential for Transmission of Antimicrobial Resistance in the Food Chain

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Quote from Alexander Fleming's 1945 Nobel Prize Lecture

"But I would like to sound one note of warning. Penicillin is to all intents and purposes non-poisonous so there is no need to worry about giving an overdose and poisoning the patient. There may be a danger, though, in underdosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.

The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death? Why Mr. X whose negligent use of penicillin changed the nature of the microbe. Moral: If you use penicillin, use enough."

Nobel Lectures, Physiology or Medicine 1942-1962, Elsevier Publishing Company, Amsterdam, 1964

Source: "Sir Alexander Fleming - Nobel Lecture: Penicillin".
Nobelprize.org. Nobel Media AB 2014. Web. 8 Oct 2015.

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FOREWORD

In 1929, Alexander Fleming identified the first antibiotic, penicillin. In his 1945 Nobel Prize lecture, Fleming reminded the world of the need to use antibiotics cautiously to ensure their continued effectiveness. The rise in antimicrobial resistance (AMR) is now recognised worldwide as one of the greatest potential threats to human and animal health, with possible serious consequences for public health, animal welfare and the agri-food sectors.

In 2014, the Irish Government published a National Risk Assessment (NRA) document. The purpose was to identify strategic risks which might have an adverse impact on Ireland's well-being and ensure appropriate prevention and mitigation frameworks are in place. Antimicrobial resistance was identified as a national risk in both the 2014 and again in the draft 2015 NRA document. These documents recognise that the advances achieved as a result of the use of antimicrobial agents are now seriously in jeopardy because of the emergence and spread of resistant bacteria against which an increasing number of antimicrobials are ineffective. The documents highlight that if the level of AMR continues to rise, it will become increasingly difficult and expensive to control and treat infections in medical care and more difficult to maintain animal health and welfare.

It is well established that bacteria frequently transfer between humans, animals and the environment. These interconnections between human and animal health and the environment are recognised in the 'One Health' concept, which promotes the importance of collaborative efforts to attain optimal health for all three. The concept is supported by global animal health (OIE) and human health agencies (WHO) and has an important role in the control of antimicrobial resistance. In 2014, the Minister for Agriculture, Food and the Marine, Simon Coveney, T.D. and the Minister for Health, Leo Varadkar, T.D. recognised the need for a coordinated 'One Health' approach for Ireland and established a National Interdepartmental Antimicrobial Resistance Consultative Committee to tackle the growing problem of antimicrobial resistant bacteria.

The objective of this report of the Scientific Committee of the Food Safety Authority of Ireland is to focus on the potential for transmission of AMR through the food chain, while recognising the interconnectedness between the food chain, the environment and humans, and to identify control strategies.

The Scientific Committee would like to especially acknowledge the work of the Biological Safety Subcommittee and the expert Working Group in contributing to this report.

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ABBREVIATIONS

ABP
Animal by-product

AMR
Antimicrobial Resistance

CDC
Centers for Disease Control and
Prevention

CIA
Critically important antibiotics

CVRL
Central Veterinary Research
Laboratory (Ireland)

DAFM
Department of Agriculture, Food and
the Marine

DANMAP
Danish Integrated Antimicrobial
Resistance Monitoring and Research
Programme

DEFRA
Department for Environment Food
and Rural Affairs (UK)

EARS
European Antimicrobial Resistance
Surveillance

ECDC
European Centre for Disease
Prevention and Control

EFSA
European Food Safety Authority

EMA
European Medicines Agency

EMEA
European Agency for the Evaluation
of Medicinal Products

EPRUMA
European Platform for the
Responsible Use of Medicines in
Animals

ESBL
Extended-spectrum beta lactamase

ESVAC
European Surveillance of Veterinary
Antimicrobial Consumption

EU-DG SANCO
European Union Directorate General
for Health and Food Safety.
Recently renamed as EU DG SANTE

FAO
Food and Agriculture Organization of
the United Nations

GAP
Good agricultural practice

GHP
Good hygiene practice

HACCP
Hazard analysis and critical control
points

HPRA
Health Products Regulatory Authority
(formerly the Irish Medicines Board
(IMB) until July 2014)

IMB
Former name of the HPRA

MAH
Marketing authorisation holder

MRL
Maximum residue limits

MRSA
Meticillin-resistant *Staphylococcus
aureus*

NSSLRL
National Salmonella, Shigella and
Listeria Reference Laboratory

OIE
World Organization for Animal
Health

PCU
Population correction unit

RVL
Regional veterinary laboratory

USDA
U.S Department of Agriculture

VPA
Veterinary Product Authorisation

VETSTAT
Central database in Denmark to
which information is reported
by veterinarians and pharmacies.
Information includes: prescribing
veterinarian, receiving herd, product
and amount

WHO
World Health Organization

EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) is now widely acknowledged as a major global public health challenge. The priority given to dealing with this challenge is reflected in high level initiatives and policy documents such as the Irish National Interdepartmental Antimicrobial Resistance Consultative Committee, the European Commission's action plan against the rising threat of antimicrobial resistance (European Commission, 2011) and the World Health Organization (WHO) Global Strategy for Containment of Antimicrobial Resistance (World Health Organization 2001, Resolution of World Health Assembly May, 2015). The intensity of antimicrobial use and frequently inadequate standards with respect to infection prevention and control in human health systems are without question major factors in the growing problem of AMR. However, the scope of this document is limited to AMR in the food chain. It is very well established that bacteria frequently transfer between humans, animals and the environment and that many classes of antimicrobial agents are used in both humans and animals. These interconnections between human and animal health are recognised in the 'One Health' concept supported by global animal health (World Organization for Animal Health (OIE)) and human health (WHO) agencies. Therefore, although the overall importance of the food chain as a contributor to AMR in the human population is unclear, AMR must be viewed as a shared challenge which requires a vigorous response in all areas - human, veterinary and environmental.

It is important to distinguish between the issues of antimicrobial residues and AMR. Until relatively recently, the major focus of concern with respect to antimicrobial use in food production was that traces of antimicrobials administered to animals could be present in food from those animals (antimicrobial residues). This issue of residues has been addressed in the European Union (EU) through definition of maximum residue levels (MRLs) and minimum withdrawal periods. In Ireland, it is very unusual to find food products that contain antimicrobials at levels above the MRL. However, antimicrobial-resistant bacteria may be present in animals and in food that are free of antimicrobial residues.

Prudent use of antimicrobials in all sectors can maximise the benefits of antimicrobials over time, while avoiding or at least delaying the development and spread of resistant bacteria. Foods may become contaminated with antimicrobial-resistant bacteria during primary production or at other stages in the process from farm-to-fork. Contamination of foods of animal origin with antimicrobial-resistant bacteria may be more likely in food from animals that have received antimicrobial agents, although antimicrobial-resistant bacteria can spread also to other animals in a herd/flock that have not received antimicrobial agents. Antimicrobial-resistant bacteria may persist in the indoor or outdoor environment for long periods when animals are no longer present. Foods of non-animal origin may be contaminated through land-spreading of organic materials, such as manures or municipal sludge, or through contaminated irrigation water. For food that is produced in Ireland, there is potential for action to influence the process of primary production. The processes of primary production for imported food are not under direct control of Irish authorities. There is no evidence to show clearly if imported food represents a greater risk than domestically produced food, but it is important that imported food should be included when assessing AMR in the food chain. As there is no EU standard for antimicrobial-resistant bacteria in food, considerations for sampling for AMR are not part of the border control process.

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Measures aimed at reducing or eliminating pathogens and indicator organisms from food, i.e. good agricultural practices (GAP), good hygiene (GHP) and Hazard Analysis and Critical Control Point (HACCP)-based procedures should substantially reduce the risk of transmission of viable antimicrobial-resistant bacteria through the food chain. For example, good hygiene during slaughter and carcass dressing can minimise transfer of bacteria including antimicrobial-resistant bacteria. Foods that are cooked/pasteurised or receive other microbiocidal treatment, e.g. high pressure processing, are unlikely to carry viable antimicrobial-resistant bacteria derived from primary production. In addition to antimicrobial-resistant bacteria derived from primary production, there is potential for cooked or processed foods to become contaminated during storage, preparation and serving. Drinking water can act as a direct vehicle for transmission of antimicrobial-resistant bacteria when contaminated with animal or human faeces. Waterborne contamination may also arise during primary production, e.g. irrigation water on crops, or food processing, e.g. as an ingredient.

To manage the risk of AMR in the food chain, it is important to monitor both (1) the use of antimicrobial agents in food production and (2) the occurrence of AMR in bacteria from food animals and food. Ireland, like other EU countries, is required by EU legislation (Directive 2003/99/EC and since 1st January 2014 Commission Implementing Decision 2013/652/EU) to undertake monitoring of AMR in specific zoonotic pathogenic bacteria and in specific indicator organisms isolated from animals and food of animal origin. The results from this monitoring are published by the European Food Safety Authority (EFSA) as annual EU Summary Reports on AMR in zoonotic and indicator bacteria from humans, animals and food. The requirements on AMR monitoring have become more stringent and harmonised with regard to tested organisms, sample populations, methodology and interpretative criteria used. In Ireland, the situation regarding AMR in meat-producing animals and food of animal origin is broadly comparable with that of most other European countries. Antimicrobial resistance is common in both zoonotic pathogens, e.g. *Salmonella* and *Campylobacter*, and indicator organisms, e.g. *E. coli*. Information on AMR in food of non-animal origin, including water, is very limited and primarily from research papers.

Antimicrobial use in food animals occurs in the context of the regulatory framework for animal remedies. Data on antimicrobial use in animals in Ireland, as in many other countries, are limited because the data collected are sales data, rather than actual usage data, and are not animal specific. Similarly at EU level, a major limitation of the data collected by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) is the fact that it is based on total antimicrobial sales (as opposed to actual use) per country and these are not broken down by animal species. However, some indicative information can be obtained by examining the antimicrobial sales data. The total tonnage of antimicrobials sold for veterinary use in Ireland in 2013 was 100 tonnes, which was an increase on the figure of 97.4 tonnes sold in 2012 and of 85.2 tonnes reported for 2011. The bulk of sales were of the 'older antibiotics', which have been used in human and veterinary medicine for decades: penicillins, tetracyclines, sulphonamides and aminoglycosides.

Antimicrobial use in intensively farmed animals is usually greater than in other production systems. Data available allow one to estimate that antimicrobial use in pig production in Ireland in 2011 was in the range of 96.6 to 152.5 mg/kg pig meat. Danish data indicate a figure of 40 mg of antimicrobial agent/kg pig meat produced in 2011. Estimates suggest that antimicrobial use in the poultry sector in Ireland is considerably higher than in Denmark, although information from specialist poultry practitioners suggests that use in broiler production is low in Ireland.

In order to improve surveillance data on usage, ESVAC, proposes that data are provided which *"will be the prescribed or estimated amounts used, in weight of active ingredient, by country and year for each product (name and pharmaceutical form or administered route) per defined animal species and weight group/production type"* (European Medicines Agency, 2013). It is further suggested that the unit of measurement should be 'defined daily dose animals' which is similar to the 'defined daily dose' used to measure antimicrobial consumption in humans, thus enabling analysis of human and animal consumption data together. A pilot programme is currently underway in selected EU Member States in which data on antimicrobial use in pigs are being collected.

Policies and actions related to control of antimicrobial use and AMR in the food chain have been developed in many individual countries and through inter-country cooperation at many levels, both European and global. To inform the development of policies and actions for Ireland, an overview of the international response and a summary of the Danish approach, a country with many years of experience in tackling this issue, are presented in Chapter 6.

The main conclusions of this report are that antimicrobial-resistant bacteria are transmitted to humans through the food chain, although the contribution of this transmission pathway to the overall problem of AMR in humans is not readily quantified. Measures aimed at reducing or eliminating bacteria from food, e.g. cooking, good hygiene practice, can be expected to substantially reduce the risk of transmission of antimicrobial-resistant bacteria through the food chain. Antimicrobial resistance is driven by antimicrobial consumption; there is intense use of antimicrobials in at least some sectors of primary food production in Ireland, and there is scope to reduce use. This is required as part of an all-sector response to reduce and improve antimicrobial use, and the National Interdepartmental Antimicrobial Resistance Consultative Committee is a key structure to manage this process. There are gaps in current systems for surveillance of antimicrobial use in food production and of AMR in the food chain, and integration and analysis of human and non-human antimicrobial resistance data are lacking.

A key recommendation includes reducing the demand for antimicrobial use in primary production by improving preventive measures. When required, prudent use of antimicrobial agents should be supported by improving training and therapeutic guidelines, equivalent regulatory control of all antimicrobial formulations, developing targets and incentives for each animal sector to drive more prudent use and by developing systems that allow more targeted delivery of antimicrobial agents to the animals that actually need to receive them. Systems to improve surveillance of antimicrobial use and of AMR should be further developed and findings published annually as an integrated human and food chain report.

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CHAPTER 1. INTRODUCTION

1.1   The Scale of the Antimicrobial Resistance Problem

Antimicrobial resistance (AMR) is now widely acknowledged as a major global public health challenge (FAO/ WHO/OIE, 2007; WHO, 2011b; WHO, 2014). Only a brief indication of the scale of the problem in Ireland is provided here. Currently In Ireland, data from the Health Protection Surveillance Centre (HPSC) and the European Antimicrobial Resistance Surveillance Network (EARS-Net) reports provide some good news in that the proportion of *Staphylococcus aureus* blood stream infections caused by methicillin-resistant *S. aureus* (MRSA) has declined in recent years (HPSC, 2014). The annual report of the Methicillin-Resistant *Staphylococcus aureus* reference laboratory indicates that MRSA from humans in Ireland is almost entirely accounted for by a limited number of clonal groups circulating in the population (National Meticillin-Resistance Staphylococcus Reference Laboratory, 2013). In contrast with *S. aureus* however, there is little good news in relation to AMR in other common bacteria. For example, the proportion of blood stream isolates of *E. coli* and *Klebsiella pneumoniae* resistant to cephalosporins and fluoroquinolones is increasing. In 2004, in the case of *E. coli*, levels of resistance to cephalosporins and ciprofloxacin were at 2.6% and 12.6% respectively. In 2014, the corresponding figures were at 12.9% and 26.2% (HPSC, 2014). One of the most serious antimicrobial-resistant problems facing Europe at present, carbapenemase-producing Enterobacteriaceae (CPE), is now also well established in Ireland (ECDC, 2011; National Carbapenemase Producing enterobacteriaceae (CPE) Reference Laboratory Service, 2015). Antimicrobial resistance in foodborne pathogens such as *Campylobacter* and *Salmonella* is also a significant problem. In Ireland in 2013, 30% of human isolates of *salmonella* were multi-drug resistant and 15.9% were resistant to ciprofloxacin (National *Salmonella*, Shigella and Listeria Reference Laboratory, 2013). There is no national reference laboratory service for *Campylobacter* spp. samples from humans in Ireland. However, data for *Campylobacter* spp. from food animals indicate that resistance to fluoroquinolones is common in isolates from pigs and poultry (McGill *et al.*, 2006).

Estimates for the number of infections and deaths associated with antimicrobial-resistant bacteria in Ireland are not available. The European Centre for Disease Control (ECDC) however, estimates 25,000 deaths per year associated with AMR and €1.5 billion in health care costs and lost production for the European Union (EU) as a whole (ECDC/ EMEA, 2009). The USA estimates that two million people are infected annually with antimicrobial-resistant bacteria and that there are 23,000 associated deaths per year (Centers for Disease Control and Prevention (CDC), 2013). A crude extrapolation based on population size for Ireland may suggest the order of 30,000 infections per year and 250 - 500 deaths.

The priority now given to dealing with this challenge is reflected in high level policy documents such as the European Commission action plan against the rising threat of AMR (European Commission, 2011) and the WHO Global strategy for the containment of AMR (WHO, 2015). As is clear from the major European and global policy documents, AMR is a complex problem (United States Department of Agriculture, 2014; Directorate General of Health Services Ministry of Health and Family Welfare, 2011; Department of Health and Department for Environment Food and Rural Affairs, 2013; WHO 2015). The intensity of antimicrobial use and inadequate standards with respect to infection prevention and control in human and animal health systems are without question major factors and key foci for intervention. The scope of this document however, is limited to AMR in the food chain. The focus is therefore, on antimicrobial use in food production although recognising that antimicrobial use in human health systems also has the potential to contribute to AMR in the food chain.

1.2   Human and Animals – The 'One Health' Concept

In many instances, antimicrobial agents of the same class are used in both human and animal medicine. Likewise, many important species of bacteria, e.g. *E. coli*, *Salmonella enterica*, *Campylobacter* spp. and *S. aureus* occur and cause disease in both humans and animals. It is very well established that bacteria of these species frequently transfer between humans, animals and the environment. These interconnections between human and animal health and the environment are recognised in the 'One Health' concept, which promotes the importance of collaborative efforts to attain optimal health for all three. The concept is supported by global animal health (OIE) and human health agencies (WHO) (ECDC, 2012; OIE/WHO, 2012; WHO 2015; Department of Health and Department for Environment Food and Rural Affairs, 2013; United States Department of Agriculture, 2014).

In keeping with this, it is increasingly recognised that acquired AMR (see Section 1.3.6) in humans and animals is interconnected. Acquired AMR makes it more difficult to treat infection in both veterinary and medical practice. Therefore, AMR must be viewed as a shared challenge which threatens the sustainability of health care in both medical and veterinary practice and which requires a vigorous response in all areas - human, veterinary and environmental.

1.3   The Background to the Antimicrobial Resistance Problem

Several comprehensive descriptions of the biological aspects of AMR have been produced by international organisations such as WHO, FAO, OIE, ECDC and EFSA. The purpose of this section is to summarise briefly some important background information relevant to the scope of this document.

Any compound that is generally toxic for microbial cells may be said to have antimicrobial activity. Any given compound may be effective against some bacteria (sensitive/susceptible bacteria) but not against others (resistant bacteria). The focus of public health concern with respect to antimicrobial-resistant bacteria is in relation to therapeutic antimicrobial agents, that is to say those agents that are used to treat and prevent infection in humans and/or animals. Therapeutic antimicrobial agents are often referred to as 'antibiotics'. Others may use the term 'antibiotic' to refer only to naturally occurring antimicrobial compounds. The terms antimicrobial and antimicrobial agents are now generally used in European and global documents and will be used in this report. Antimicrobial agents have played and continue to play important roles in human and animal health care. They are of value in the treatment of bacterial infection and also for certain applications in the prevention of infection. In many settings, antimicrobials have a vital enabling effect with respect to other treatments applied in human health care such as cancer treatment. This is because antimicrobials can be used to prevent and to manage infectious complications associated with the other treatments.

1.3.1   Antimicrobial resistance and antimicrobial agents

Antimicrobial resistance refers to reduced sensitivity or complete insensitivity of some microorganisms to one or more antimicrobial agents (WHO, 2001b). This report is principally concerned with resistance to therapeutic antimicrobials. Therapeutic antimicrobials are compounds which, at low concentrations, can interact with and disrupt specific biochemical pathways in critical processes of particular bacteria (Leekha *et al.*, 2011). Through this action, they kill the bacteria or prevent the bacteria from growing. Therapeutic antimicrobials ideally have little or no toxic effect on the critical functions of animal cells at the concentration that is needed to impact on target bacteria. This ability to target a particular process in bacteria is the basis for the selective toxicity of antimicrobial agents. In addition to those agents designated as antibacterial agents, compounds designated as coccidiostats are also used in food animal production. Coccidiostat treatments are promoted for treatment of protozoan parasite infection rather than bacterial infection, however many of the coccidiostats have activity against bacteria. In poultry production, an antibacterial effect of coccidiostats administered to poultry is an intended secondary gain from the use of these agents. Coccidiostats are not expressly considered in this report, however a contribution by compounds designated as coccidiostats to selection for AMR in bacteria is plausible (McEwen & Fedorka-Cray 2002).

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1.3.2   Classes of antimicrobial agents

There are many different antimicrobial agents but it is possible to group them into classes of similar compounds. For example, benzylpenicillin, ampicillin and piperacillin are three antimicrobials that are all in the class of penicillins (Table 1.1). All of the penicillins, together with all of the cephalosporin antimicrobials, comprise the beta-lactam class. The class concept is important because antimicrobials in the same class generally act on the same critical target in bacteria. Therefore, if bacteria that are resistant to one member of the class emerge, those bacteria tend to be less susceptible also to some or all of the other members of the same antimicrobial class. To a greater or lesser extent therefore, use of any member of a class of antimicrobials tends to favour the emergence of bacteria that are resistant to all members of that class (Anderson *et al.*, 2002; WHO, 2011b).

Table 1.1 Classes of some common antimicrobial agents and their mechanisms of actions
(adapted from Anderson *et al.*, 2012)

Class	Example	Mechanism of Action
Penicillins	Methicillin, Benzylpenicillin, Ampicillin and Piperacillin	Inhibits cell wall synthesis (Beta-lactams and related)
Cephalosporins (1st, 2nd 3rd and 4th generation)	Cefazolin (1st), Cefaclor (2nd), Cefotaxime (3rd), Cefepime (4th)	
Carbapenems	Meropenem	
Glycopeptides	Vancomycin	Other cell wall inhibitors
Aminoglycosides	Gentamicin	Protein synthesis inhibition (30S ribosomal subunit)
Tetracyclines	Tetracycline	
Macrolides	Erythromycin	Protein synthesis inhibition (50S ribosomal subunit)
Chloramphenicol	Chloramphenicol	
Quinolones/ Fluoroquinolones (1st, 2nd 3rd and 4th generation)	Nalidixic acid (1st), Ciprofloxacin (2nd), Gaifloxacin (3rd), Gemifloxacin (4th)	DNA synthesis inhibitors

A further complication in this regard is the extent to which genes encoding for resistance to antimicrobials tend to group together to form large highly mobile genetic elements that encode for resistance to many different antimicrobial classes. These mobile genetic elements may also include genes for resistance to substances such as disinfectants and heavy metals. Exposure to any one of the classes of antimicrobials, disinfectants or heavy metals in question will tend to support retention by bacteria of that entire multifunctional genetic element. Therefore, to some extent, almost all antimicrobial agents and disinfectants can contribute to the problem of increasing AMR.

1.3.3   Critically important classes of antimicrobials

Antimicrobials have been in general use in human and animal medicine for more than 70 years. Acquired resistance to some agents is already widespread to such an extent that the value of those agents for treatment of life-threatening infection is already greatly reduced, e.g. tetracycline and sulphonamide (EFSA, 2008; Prendergast *et al.*, 2009; WHO 2011a). There are a number of newer antimicrobials that play a critically important role in the treatment of serious infection and for which good alternative treatments may be limited, e.g. third generation cephalosporins, floroquinolones, carbapenems. In many cases, the reliability of these critically important antimicrobials is already reduced or under serious threat because of increasing levels of acquired resistance. Prudent use of these critically important agents takes priority over other, often older agents. This is one of the important reasons why simple

comparisons based on tonnes of antimicrobials used in humans and animals are of limited value. Use of a tonne of an older agent such as tetracycline does not equate to use of a tonne of a critical reserved agent such as meropenem. Nevertheless, as outlined earlier, because AMR genes tend to be grouped together on large mobile elements, all antimicrobial classes have the potential to contribute to some degree to selection of cross-resistance to other classes.

The WHO and the OIE have produced a list of critically important antimicrobials for human and veterinary medicine, respectively (OIE, 2007; WHO 2011a). Both lists are periodically reviewed. In the case of human medicine, aminoglycosides, carbapenems, third and fourth generation cephalosporins, fosfomycin, fluoroquinolones, glycopeptides, glyclyglycines, lipopeptides macrolides and ketolides, monobactams, oxazolidinones, penicillins, polymyxins and rifamycins are considered critically important antimicrobial agents (WHO, 2011a).

1.3.4   Measuring the activity of antimicrobial agents against particular bacteria

The principal numerical value used to represent the activity of a particular antimicrobial against a particular culture of bacteria is the minimum inhibitory concentration (MIC). The MIC is the lowest concentration of the antimicrobial that prevents the bacteria in question from growing under defined conditions that would support rapid multiplication of the bacteria in the absence of antimicrobial (EFSA, 2008; Anderson *et al.*, 2012, WHO 2011b). A number of other methods to measure antimicrobial activity are also used, but these are generally calibrated against methods for measuring MIC. In general, the lower the MIC the more *'sensitive'* to the antimicrobial a bacterium is and the higher the MIC, the more *'resistant'* to the antimicrobial. The sensitivity of bacteria to an antimicrobial is therefore, a matter of degrees on a scale of activity.

1.3.5   Interpreting the measurement of antimicrobial activity

The measurement of activity of an antimicrobial is expressed as an MIC along a scale of values is of limited value for clinical purposes (Kahlmeter *et al.*, 2006; Matuschek *et al.*, 2013). In both human and veterinary medicine, there is a process for reducing this complexity to discrete categories of sensitive and resistant. The process of clinical categorisation as sensitive or resistant is complex and beyond the scope of this document. The output from this process is a series of authoritative guidance documents that allow a laboratory to report a test result as sensitive or resistant. In this sense, sensitive/susceptible means that the antimicrobial will probably work to treat infection if administered in the appropriate way (dose, route, frequency and duration). If the MIC is such that the antimicrobial is unlikely to be effective in treating infection, the bacteria are considered to be resistant. The guidance documents for interpretation of a particular MIC value as susceptible or resistant, depends on the host species (human or animal) in which the antimicrobial will be used. This is the case because antimicrobials are not administered in the same way to every animal species and are not absorbed and excreted in the same way in every animal species. This can make it difficult to compare data on the percentage of bacteria categorised as resistant from humans compared with the percentage categorised as resistant from an animal species. For example, 30% of human *E. coli* isolates resistant to an antimicrobial may not mean the same thing as 30% of poultry *E. coli* isolates resistant to the same antimicrobial. There can also be difficulties in comparing data on categories of sensitive and resistant microorganisms, even from the same bacterial species, where countries are using different sets of criteria for classifying the MIC value as susceptible or resistant, although many of the differences have reduced in recent years.

1.3.6   Ecological cut-off values

One solution to the lack of uniformity of clinical criteria for categorisation of bacteria as susceptible or resistant, is to collect and compare the actual MIC value where these are available. Another approach is to define for each species of bacteria, e.g. *E. coli*, the highest MIC value that was observed among that species when the antimicrobial was new, and therefore, before any genetic change related to the antimicrobial use had become established in the wild type global bacterial population. This value is known as the Ecological Cut-off (ECOFF) value (Kahlmeter *et al.*, 2006). The ECOFF value is specific to a particular species of bacteria, e.g. *E. coli*, and a particular antimicrobial, e.g. ciprofloxacin.

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This ECOFF value applies regardless of where in the world or from what host species the bacteria have been cultured. The ECOFF value is not always directly related to the clinical interpretation of susceptible or resistant bacteria although it is one important element in guiding this. In general, changes in clinical interpretive criteria in recent years have resulted in closer alignment of clinical break points with ECOFF values (Matuschek *et al.*, 2013). Bacteria with MIC values below the ECOFF are considered 'wild type' and those with values above the ECOFF value are considered 'non-wild type'. 'Non-wild' type bacteria represent populations of bacteria that have undergone some genetic change that increases their ability to withstand the action of the antimicrobial in question (Chen *et al.*, 2015). If over time, there is an increase in the proportion of a particular species of bacteria that are 'non-wild' type for a particular antimicrobial, this indicates progression towards the loss of effectiveness of that antimicrobial, even if the bacteria have not crossed the threshold MIC value used to categorise it as resistant for clinical purposes. Therefore, increases in the percentage of 'non-wild' type bacteria are of concern for human and animal public health and are potentially the most sensitive indicator of emerging problems of resistance.

1.3.7   Intrinsic and acquired antimicrobial resistance

For any particular antimicrobial there are some species of naturally occurring bacteria against which that antimicrobial, from the outset, has little or no activity. This is referred to as 'intrinsic AMR' (Anderson *et al.*, 2012; Chen *et al.*, 2015). Take for example, the environmental species *Pseudomonas aeruginosa*, which is naturally resistant to many therapeutic antimicrobial agents (Bonomo & Szabo 2006; Lister *et al.*, 2009). Bacteria with intrinsic AMR can cause serious infection in vulnerable patient groups, however the major public health concern is loss of activity of antimicrobials against those species of bacteria against which the antimicrobial was highly effective when first discovered. This is referred to as 'acquired AMR' (Anderson *et al.*, 2012; Chen *et al.*, 2015). As outlined above, the emergence and spread of all 'non-wild' type bacteria are encompassed in this concern regarding acquired resistance. This transition of bacterial populations from 'wild' type to 'non-wild' type arises because of the natural genetic flux among bacteria and the powerful selection effect of antimicrobial exposure.

1.3.8   Molecular methods for surveillance of antimicrobial resistance

There is increasing interest in recent years in the use of molecular methods to detect genetic changes that result in increasing resistance to antimicrobials. The pace of technological change in this respect is very rapid. Molecular methods are already very important in research and surveillance of AMR and are in routine use for laboratory detection and confirmation of AMR in some settings. These methods are likely to become increasingly important in the next decade (Anderson *et al.*, 2012; Chen *et al.*, 2015).

1.4   Genetic Diversity, Genetic Determinants and Change in Bacteria

The natural world of bacteria is highly diverse and in a constant state of genetic change. This includes random point changes in DNA sequence but also transfer of large genetic elements between bacteria (WHO, 2011b). Exchange of DNA can occur even between species of bacteria that are very different from each other, thus generating new variant bacteria with novel properties. Some have described this as being like a genetic cloud of information from which individual bacterial cells randomly download new information. If a genetic change results in a new variant that can outgrow and divide faster than other bacteria in its immediate niche, then that variant tends to take over the niche. This reflects Darwin's theory of natural selection. This successful variant may then spread from that niche to other places (Tenover, 2006).

Therefore, in addition to the concerns regarding viable antimicrobial-resistant bacteria, there are also concerns regarding genetic elements/fragments of DNA that encode for determinants of AMR. Free DNA coding for AMR may, under certain circumstances, be assimilated into the genome of viable bacteria, thus conferring acquired resistance on those bacteria.

1.5   Selection for Antimicrobial Resistance

For any given antimicrobial class it is almost inevitable that at some point a random genetic change will result in a new variant of a previously very sensitive species of bacteria that is less vulnerable to the action of the antimicrobial ('non-wild' type bacteria). When this happens in a niche where an antimicrobial of that class is present, e.g. a human or an animal taking an antimicrobial from that class, there is a very powerful selection effect. The 'wild' type bacteria present in the niche are rapidly killed by the antimicrobial and the new 'non-wild' type variant multiplies rapidly to fill the gap left by the death of the 'wild' type. Although this may occur in any setting in which antimicrobials occur, the gastrointestinal tract is thought to be important for a number of reasons (Buffie & Pamer, 2013):

1. The gastrointestinal tract has a very large and diverse bacterial population

2. When antimicrobials are administered they are often present in the gastrointestinal tract because they are often administered by mouth

3. New bacteria and new DNA frequently enter the gastrointestinal tract

4. Bacteria present in the gastrointestinal tract are shed in very large numbers in the faeces, they can heavily contaminate other surfaces and matrices and may spread to the gastrointestinal tract of others

1.6   Surveillance of Antimicrobial Resistance in Ireland and Europe

There is extensive research providing snapshots of the prevalence of resistance to antimicrobials in particular location and time, and the underlying genetic mechanisms (Tyne & Gilmore 2015; Bonnin *et al.*, 2013; Kos *et al.*, 2012; Lam *et al.*, 2012). Such research papers represent an important perspective on this problem, but it can be difficult to form an overview of change over time from this research because the work tends to lack long term continuity and in addition, sampling and analytical methods may vary. Structured continuous surveillance of resistance, with some degree of standardisation of methods, is essential to form a coherent picture. This document relies heavily on data from structured surveillance activities. The most important sources of surveillance in this regard at the EU level are the joint ECDC/EFSA annual reports on AMR in zoonotic bacteria, i.e. bacteria that can be transmitted from animals to humans, and the EARS-Net programme of surveillance of AMR in certain species of bacteria isolated from human blood cultures. Ireland contributes data to both of these activities (EFSA, 2015).

1.7   Prudent Use of Antimicrobials – Definition

It follows from the above that in general terms, the more often and the more widely an antimicrobial class is used, the more quickly 'non-wild' type variants are likely to develop and spread. Essentially, all antimicrobial use drives the selection of increasingly resistant variants of bacteria. However, care in the use of antimicrobials can maximise the benefits of antimicrobials while avoiding or at least delaying the development and spread of resistant variants. Different terms are used to encapsulate the idea of making the best use of antimicrobials while minimising the selection of acquired AMR. The terms 'responsible use', 'prudent use' and 'antimicrobial stewardship' are used. While the terms are closely related, they may each convey a somewhat different emphasis and each term has its merits. For the purposes of this report, the term 'prudent use' will be used for consistency because this term has been adopted in a number of key EU policy documents relating to antimicrobial use (Commission Decision 2013/652/EU; Scientific Committee on Emerging and Newly Identified Health Risks 2012; European Commission, 2015a; EFSA, 2004; EFSA, 2009; European Commission, 2011; EFSA, 2008; ECDC, 2012). Antimicrobial use is accepted as the key driver of acquired AMR and surveillance of antimicrobial use is important in understanding the problem and in measuring the success of policies intended to improve use. A number of organisations have produced guides to prudent use, including the European Commission (2015).

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1.8   Surveillance of Antimicrobial Use in Ireland and Europe

Surveillance of antimicrobial use in both humans and animals is important. The principal value of surveillance is to support and to document prudent antimicrobial use (overall reduction and more targeted application) in all sectors. Simplistic comparisons of baseline antimicrobial use in terms of tonnes used in humans, compared with tonnes used in animals, are of little value and tend to be divisive. Such comparisons do not capture differences in the number of humans and animals, differences in potency, dosage and environmental persistence of compounds and the patterns of disease in the different sectors. In particular, such comparisons do not reflect the distinction between critically important classes of antimicrobials and those classes of antimicrobials that are now less important for treatment of human infection.

1.9   Antimicrobials and the Food Chain

Until relatively recently, the major focus of concern with respect to antimicrobial use in food production was that traces of antimicrobials administered to animals could be present in food, in particular in meat and milk and in products derived from meat and milk. This issue has been addressed in the EU through the definition of minimum periods (withdrawal periods) that must elapse between administering an antimicrobial to an animal and the use of products from that animal for food (Directive 2001/82/EC). This policy is reinforced in the EU by a programme of testing of samples of products for antimicrobials. In Ireland, it is very unusual to find food products that contain antimicrobials at levels above the defined thresholds (Department of Agriculture, Food and the Marine, 2013).

1.10   Antimicrobial-resistant bacteria and the Food Chain

Although withdrawal periods are generally effective in ensuring that antimicrobials in animals fall below acceptable thresholds before food products are derived from them, absence of antimicrobial agents does not mean that resistant bacteria will have disappeared from the animal during the withdrawal period. Once antimicrobial-resistant bacteria have become established in an animal, they may persist for long periods after the antimicrobial has become undetectable in the animal's body. Foodborne transmission of antimicrobial-resistant bacteria from food animals to people is well documented (Codex Alimentarius Commission, 2011; WHO 2011b; EFSA, 2008). There are also other potential sources of antimicrobial-resistant bacteria in food. Antimicrobial-resistant bacteria in contaminated water used to irrigate or wash food are another source. Food workers who carry antimicrobial-resistant bacteria may also have the potential to contaminate food with these bacteria through poor handling. Contamination of the food processing or food preparation environment with antimicrobial-resistant bacteria represents another potential source. Thorough cooking is, of course, as effective in destroying antimicrobial-resistant bacteria as it is in destroying 'wild' type bacteria. However, not all foods are cooked and cooking is not always thorough.

AMR has been described in many different species of bacteria. Meticillin-resistant *Staphylococcus aureus* (MRSA) is one of the best known examples. There are reports that MRSA colonisation of food animals, particularly pigs, is common in some countries and that this phenomenon is associated with distinct clonal groups. Occupational transmission of MRSA from food animals to humans is well documented and transfer of MRSA through the food chain has also been documented (Hanselman *et al.*, 2006; Lewis *et al.*, 2008). At present in Ireland, MRSA in humans is primarily related to person-to-person transmission of human associated clonal groups (National Meticillin-Resistant *Staphylococcus aureus* Reference Laboratory, 2013). For the purposes of this report, the emphasis will be on two foodborne pathogens (*Salmonella enterica* and *Campylobacter* spp.) and two indicator organisms (*E. coli* and *Enterococcus* spp.).

1.10.1 Antimicrobial-resistant genes and food

Even when antimicrobial-resistant bacteria in food are killed by heat, it is possible that genetic sequences encoding resistance remain intact. This DNA may form part of the genetic cloud from which resident gut bacteria have the potential to 'download' new genetic information. There is little information to indicate to what extent if any, this repository of resistance genes is present, intact and available in food and animal feed, and there is even less information regarding the extent to which it may contribute to acquired AMR in the gut (Buffie & Pamer, 2013). A related area of potential concern is AMR genes that are inserted synthetically into plant cells in development of genetically modified food crops (EFSA, 2004; EFSA, 2009).

1.11 Summary

Antimicrobial resistance is a major public health problem. The biology of this process is relatively well understood. The intrinsic adaptability of bacteria, the intensity of use of antimicrobial agents and practices which support spread of bacteria from host-to-host are key drivers. The intensity of antimicrobial use and the pathways of spread of bacteria are those areas where intervention is possible, but effective action has been slow in both domains. Although the relative importance of the food chain is uncertain, use of antimicrobials in food production and the potential for spread of bacteria from host-to-host through the food chain are areas of concern. This report aims to address these issues from the perspective of the food chain in Ireland.

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CHAPTER 2. TERMS OF REFERENCE

Context

Acquired AMR is a major global public health concern and is related to the use of antimicrobial agents. In 2011, the EU Commission published a 12 point action plan to tackle the problem with respect to both human and veterinary medicine (European Commission, 2011). A number of Irish agencies/bodies[1] have formed Working Groups or Committees to address AMR. The Food Safety Authority of Ireland (FSAI) has requested its Scientific Committee to examine the issue with respect to the potential for transmission of antimicrobial-resistant bacteria and genetic determinants of resistance in the food chain. The Scientific Committee has delegated the task to its Biological Safety Sub-committee. In developing its report on this issue, the Scientific Committee acknowledges and draws on the work of other agencies/bodies in this area and will minimise duplication by keeping its focus on the food chain.

> For the purposes of this report therefore, AMR refers to acquired AMR in bacteria and DNA with the potential to transfer resistance to bacteria.

Included in the scope:

- Potential for transmission of AMR *via* foods of animal and non-animal origin

- Potential for transmission of AMR from imported as well as domestically produced food

- Potential for transmission of AMR as a result of contamination of food between production and consumption, e.g. from food workers

- Focus on antimicrobial agents of greatest importance to human health including those antimicrobial agents that select for cross-resistance to agents important for human health

- Focus on resistance in *Salmonella*, *Campylobacter* and the indicators *E. coli* and *enterococci*

- Potential for transmission of AMR by bacterial cultures used in food production

- Possible impact of biocides (used on surface and incorporated into equipment and packaging) and other stresses during processing on potential transmission of AMR

- Potential for transmission via genetically modified plants carrying AMR gene markers

Excluded from the scope:

The following are excluded from the scope however, they may be referred to as appropriate to provide context

- Human-to-human transmission of antimicrobial-resistant bacteria independent of the food chain

- Transmission of antimicrobial-resistant bacteria from companion animals

- Transmission of antimicrobial-resistant bacteria from food-producing animals that is independent of the food chain, e.g. occupational exposure

2.1   Chapter Bibliography

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[1]   The Department of Agriculture Food and Marine, Veterinary Ireland and the Royal College of Physicians of Ireland have set up Working Groups/ Committees to address AMR in veterinary and human medicine. The Animal and Plant Health Association is facilitating a group to look at the Responsible Use of Medicines in Agriculture Alliance (RUMA). In 2014, the Ministers for Health and Agriculture set up the National Interdepartmental Antimicrobial Resistance Consultative Committee.

CHAPTER 3. REVIEW OF POTENTIAL ROUTES OF TRANSMISSION AND METHODS OF PREVENTION OF ANTIMICROBIAL RESISTANCE IN THE FOOD CHAIN

3.1   Introduction

People can potentially be exposed to antimicrobial-resistant bacteria in the food chain in a number of ways which will be discussed in this chapter. In EFSA's 2008 review of foodborne AMR as a biological hazard, it found that the present extent of exposure to antimicrobial-resistant bacteria via the food chain was difficult to determine, and the role of food in the transfer of resistance genes was insufficiently studied (EFSA, 2008). However, it concluded that any further increase in the occurrence of antimicrobial-resistant bacteria in food is likely to have an influence on human exposure. This chapter outlines potential transmission routes and methods of control of AMR in the food chain. Figure 3.1 (adapted from EFSA (2008)) illustrates the potential pathways by which veterinary and human antimicrobial use may contribute to the presence of antimicrobial-resistant bacteria in the food chain. It identifies the links between humans, animals and environment and illustrates the importance of the 'One Health' concept (Section 1.2).

Figure 3.1. Potential routes of transmission of antimicrobial-resistant bacteria via the food chain (EFSA, 2008)

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3.2 Potential Routes of Transmission of Antimicrobial Resistance in the Food Chain

3.2.1 Overview

Raw or undercooked foods are much more likely than cooked food to contain bacteria, including antimicrobial-resistant bacteria, derived from primary production (Rosenquist *et al.*, 2005; Meldrum *et al.*, 2005; Luber *et al.*, 2006; Bohaychuk *et al.*, 2009; Hansen *et al.*, 2010; Losio *et al.*, 2015). Foods that are cooked, or receive other microbiocidal treatment, e.g. high pressure processing, are unlikely to carry antimicrobial-resistant bacteria derived from primary production but intact DNA coding for resistance if present, may persist in such food (EFSA, 2008). The potential for uptake by bacteria in the human gut of resistance genes in food is uncertain. In addition to antimicrobial-resistant bacteria derived from primary production, there is potential for cooked or processed foods to become contaminated during storage, preparation and serving.

i. Foods of animal origin

Foods of animal origin are considered to be an important source of antimicrobial-resistant bacteria entering the food chain (EFSA, 2008). The principal focus of concern is antimicrobial-resistant bacteria acquired by the animal on the farm. In addition, foods of animal original may also act as a potential vehicle for human-to-human transmission of antimicrobial-resistant bacteria.

The zoonotic pathogens of primary concern with regard to AMR in Ireland at present are *Salmonella* and *Campylobacter*. Based on European surveillance data, contaminated poultry meat, eggs, pork and beef are considered to be important in relation to transmission of antimicrobial-resistant *Salmonella*. A recent EU outbreak of *Salmonella* Stanley was traced to contamination in the turkey production chain (EFSA & ECDC, 2014). The isolate was resistant to nalidixic acid, however there is some evidence from a subsequent outbreak in Austria to suggest that representatives of the outbreak related clonal group also developed resistance to third generation cephalosporins and gentamicin (Springer *et al.*, 2014). In the case of antimicrobial-resistant *Campylobacter*, poultry meat is considered to be the most important potential vehicle (EFSA, 2008; EFSA, 2015). The significance of this problem is apparent from the FDA assessment of the human health impact of fluoroquinolone-resistant *Campylobacter* attributed to the consumption of chicken (Food and Drug Administration, 2000). The use of fluoroquinolones in poultry was banned in 2005 in the United States as a result of this assessment.

ii. Foods of non-animal origin

While surveillance data on the resistance to antimicrobials in bacteria from foods of non-animal origin are very limited, increasingly foods of non-animal origin are recognised as important sources of foodborne infection in Europe. Based on reported European outbreak data from 2007 to 2011 (where either foods of non-animal origin or foods of animal origin were implicated), foods of non-animal origin were associated with 10% of outbreaks (EFSA, 2013). EFSA identified the following pathogen food combinations as most important: *Salmonella* spp. and leafy greens eaten raw followed by (in equal rank) *Salmonella* spp. and bulb and stem vegetables, *Salmonella* spp. and tomatoes, *Salmonella* spp. and melons, and pathogenic *Escherichia coli* and fresh pods, legumes or grain (EFSA, 2013b). Any food that is a vehicle for pathogens must also have the potential to transmit antimicrobial-resistant bacteria. Similar to foods of animal origin, foods of non-animal origin may become contaminated with antimicrobial-resistant bacteria during primary production or at a later stage.

3.2.2   Controls of antimicrobial resistance in imported food

International trade in is an inherent part of global food security. Whilst Ireland is a net exporter of food, importation of food from other EU Member States and from third countries (outside the EU) is an important component of Irish food chain (Central Statistics Office, 2013). Within the EU, there is a single market whereby all food production should comply with a single common EU regulatory framework and therefore, can be freely traded. For third country imports to the EU, the trade is underpinned by the Sanitary and Phytosanitary Agreement of the World Trade Organization, whereby imported products should reach equivalency with the standards expected of indigenous EU-produced food.

i. Import of food of animal origin

Food of animal origin from third countries can only be imported into EU from approved processing plants (European Commission, 2006). Compliance of third country production systems with the equivalency standard is verified through audits by the Food and Veterinary Office of the EU Commission Directorate-General for Consumer Health and Protection (DG Santé). Compliance of individual food consignments is subject to official controls at the point of entry to the EU. Laboratory analysis of incoming food is carried out selectively in the EU Border Inspection Posts (BIPs) at a low frequency (European Commission, 2010). As there is no EU standard for antimicrobial-resistant bacteria in food, considerations of, or sampling for, AMR are not part of the border control process. Once a product has entered the EU it may be traded freely amongst EU Member States without further restriction. The importance of international trade in food is reflected in the data presented in Table 3.1 which shows that more meat is imported than is produced in Ireland. Much of this meat may be re-exported following further processing. Thus, imported food needs to be included in developing systems for surveillance of antimicrobial-resistant bacteria in food.

The global trend in production of food of animal origin currently shows rapid expansion. There is a growing contribution to the world market from developing countries and intensification of production systems in these countries (Narrod *et al.*, 2011). Countries have different husbandry systems with wide disparity in reliance on antimicrobial use in livestock production (Page and Gautier, 2012). The international organisation for animal health (OIE) has recognised the need to support developing countries in their efforts to address AMR (Orand, 2012). At present there is little data to indicate if there are differences in levels of AMR in home produced, compared with imported food.

Table 3.1 Figures for the main meat-producing sectors in Ireland for 2011 (Central Statistics Office, 2012)

Total animal numbers	Meat category	'000 tonnes produced	% exported	'000 tonnes home-produced sold in Ireland	'000 tonnes imported
6.5 million cattle	Beef and veal	546	93	38	57
1.5 million pigs	Pig meat	235	77	54	77
4.8 million sheep	Sheep meat	48	96	2	4
-	Poultry meat	131	82	24	91

ii. Import of food of non-animal origin

Food of non-animal origin is subject to three levels of control, depending on the level of associated risk. There is free movement within the EU of food of non-animal origin produced in the EU. Routine official controls are carried out on all products of non-animal origin (foods outside the scope of the veterinary checks legislation) entering the EU from third countries unless they are subject to increased controls or emergency measures due to risks identified. Routine official controls are organised on the basis of the Member State's multi-annual control plan in light of potential risks.

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Increased controls are carried out under Regulation (EC) No 669/2009, as amended. This requires certain foods from certain third countries to be presented for import at a Designated Point of Entry to verify compliance with specific EU legislation, e.g. mycotoxins, pesticide residues and microbiological safety. The importer must notify the competent authority in advance of the consignment's arrival. Identity and physical checks must be carried out at the frequency set. A Common Entry Document (CED) must be completed. The product can only be released for free circulation when the results of the checks carried out are satisfactory. The placing of products in Annex I of Regulation (EC) No 669/2009 is intended to be short term. Following regular review, products will either revert to routine controls as the risk has been removed, or escalated to an emergency measure.

Emergency measures are introduced under Regulation (EC) No 178/2002 or No 882/2004. In general, they require pre-export checks in the country from which the product is consigned. Consignments must be tested for compliance with EU legislation and be accompanied by certificates of analysis and health certificates. These products must also be presented at Designated Points of Entry and in some cases, on to Designated Points of Import (for products subject to aflatoxin controls) to have the necessary controls carried out to verify compliance with specific EU legislation, e.g mycotoxins, pesticide residues, microbiological safety. The importer must notify the competent authority in advance of the consignment's arrival. Identity and physical checks must be carried out at the frequency set. A Common Entry Document (CED) must be completed. The product can only be released for free circulation when the results of the checks carried out are satisfactory. These emergency measures are reviewed regularly. When and if the risk has been mitigated, the measures are realigned accordingly.

As there is no EU standard for antimicrobial-resistant bacteria in food, considerations for sampling for AMR are not part of the border control process. Once a product has entered the EU it may be traded freely amongst EU Member States without further restriction.

3.2.3   Water and primary production environment

Drinking water can act as a direct vehicle for transmission of antimicrobial-resistant bacteria when contaminated with animal or human faeces and can also be a potential vehicle for antimicrobial residues. Waterborne contamination of food may arise during primary production, e.g. contaminated irrigation water on crops, or food processing, e.g. as a contaminated ingredient.

Both human and animal by-products are a potential source of environmental contamination with antimicrobial-resistant bacteria which may impact on animal feed and food. These materials are of particular concern when spread on land in which ready-to-eat food crops are grown. Animal manures and municipal sludge (particularly sludge that contain effluents from hospitals) have been shown to contain antimicrobial-resistant pathogens and other bacteria (FSAI, 2008a; EFSA, 2008). These materials are therefore, a potential reservoir for transmission of AMR if applied on land used for food production, or discharged into waterways and estuaries serving aquaculture. The risk can be reduced if agricultural, municipal, and industrial organic materials are properly treated and in the case of ready-to-eat crops, if recommended intervals between spreading and harvesting are observed (FSAI, 2008b).

i. Containment of animal waste material

When antimicrobial agents are administered to an animal, some portion of the antimicrobial may be shed in urine, faeces and other body fluids, including milk. How these materials are subsequently handled (disposed of or recycled) may then serve to broaden the impact of the antimicrobial on selection of resistant bacteria beyond the animal to which it was administered.

Inadequate cleaning of housing between flocks and herds may help disseminate antimicrobial-resistant bacteria. Disposal of manure and slurry on farms is also a concern and is regulated under Statutory Instrument No. 610 of 2010 for the protection of waters. These regulations do not contain any reference to specific measures related to the management of waste from animals receiving antimicrobial agents. It is likely that most farmers in Ireland do not make any special provisions for manure produced by animals being treated with antimicrobials. Hölzel *et al.* found an association between the concentration of antimicrobials in slurry from pigs receiving tetracyclines and sulphonamides and levels of resistance in *E. coli* and *enterococci* isolated from the slurry (Hölzel *et al.*, 2010). Antimicrobial resistance genes were also detected more frequently in slurry samples containing antimicrobials than from samples without antimicrobials. Considerably more research is required into the impact on the environment of the disposal of slurry contaminated with antimicrobial substances.

Milk from animals which have been treated with antimicrobials and which is temporarily withheld from the human food chain as a result of this treatment, is considered to be an animal by-product (ABP). If this milk is not used or disposed of on the farm of origin, it is subject to ABP legislation (Regulation (EC) No 1069/2009). Land-spreading of such milk is permitted under Article 13 of the Regulation. Raw milk that is used or disposed of on the farm of origin is not subject to the rules in EU ABP legislation. Thus, although veterinarians and agricultural advisors discourage farmers from feeding milk from cows receiving antimicrobials to calves, this practice is permitted when it occurs on the farm of origin. This practice may be commonplace and to some degree, represents administration of antimicrobial agent to the calves. In a recent UK study, 83% of farmers fed milk from cows with mastitis to calves and only one third of these discarded the milk from the first milking after antimicrobial treatment (Brunton *et al.*, 2012). High numbers of Swedish farmers also fed milk likely to contain antimicrobial residues to calves (Duse *et al.*, 2013). The proportion of resistant faecal *E. coli* in calves fed such milk was higher than in calves fed milk without antimicrobial residues (Aust *et al.*, 2013). There are anecdotal reports of increasing use of on-farm pasteurisation for milk fed to calves. This practice, which is intended to control spread of animal disease, may help also to reduce risk of onward transmission of antimicrobial-resistant bacteria in milk but to what extent if any, it inactivates antimicrobial agents in the milk is unknown.

3.2.4   Food handlers

Infected or colonised food handlers are a potential source of antimicrobial-resistant organisms and may therefore, contaminate food. This risk is greater if they are not applying good hygienic practices. There are some reports documenting colonisation of food workers with antimicrobial-resistant *E. coli* but there is little evidence to indicate to what extent the organisms are transferred to food (Hammerum *et al.*, 2006; Price *et al.*, 2007). However, the risk is not purely theoretical as an outbreak of foodborne methicillin-resistant *Staphylococcus aureus* disease linked to a colonised food worker was reported from the United States of America (Jones *et al.*, 2002) and a foodborne outbreak of antimicrobial-resistant *Salmonella* Virchow related to a food handler has been reported from the UK (Maguire *et al.*, 2000).

3.2.5   Other less likely contributors to antimicrobial resistance in the food chain

i. Probiotic products and other fermented foods

Other potential sources of exposure to antimicrobial-resistant bacteria in foods include bacteria deliberately added to food in fermented foods and probiotic products. There are studies indicating that antimicrobial-resistant bacteria can occasionally be isolated from fermented foods (Teuber *et al.*, 1999) and products containing probiotics (Masco *et al.*, 2006). These bacteria (typically lactic acid bacteria) are not normally associated with human illness but they may infect profoundly immunocompromised people. In addition, they could potentially present an indirect hazard by acting as a reservoir of transmissible antimicrobial-resistant determinants. There is little reason at present to consider that this issue is a significant public health concern.

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ii. Genetically modified (GM) plants

Genetically modified (GM) plants have been assessed for their potential to act as a route of AMR transmission. During the production of GM plants, AMR marker genes are normally used to facilitate the identification of the modified cells. However, GM plants are not considered an important route for transmission. This is because the potential for these resistance genes to be transferred to bacteria is thought to be low as it would require a series of biologically complex and unlikely events to occur (EFSA, 2004; EFSA 2007).

iii. Emerging food processing technologies

Emerging non-thermal processing/preservation technologies, e.g. high-pressure processing, ionizing radiation, pulsed electric field and ultraviolet radiation, are designed to produce safe food, while maintaining nutritional and sensory qualities. Experimental studies suggest that such alternative preservation technologies could potentially promote the generation or transfer of AMR as a result of the damage by such technologies to cell membranes, enzymes or DNA (EFSA, 2008). The relevance of these experimental studies for industrial food processing is unknown.

iv. Biocides

Experimental studies have shown that some biocides used at sub-lethal concentrations can trigger the emergence of AMR and/or select bacteria resistant to antimicrobials. However, epidemiological evidence indicating public health relevance is lacking (Condell *et al.*, 2012; Scientific Committee on Emerging and Newly Identified Health Risks, 2012).

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CHAPTER 4. ANTIMICROBIAL RESISTANCE IN THE FOOD CHAIN IN IRELAND

Ireland, like other EU countries, is required by EU legislation (Directive 2003/99/EC) and since 1st January 2014, (Decision 2013/652/EU) to undertake monitoring of AMR in zoonotic agents and indicator organisms isolated from animals and food of animal origin. Continuous and updated information on AMR is essential to guide risk profiling, risk assessment and risk management, and to determine the effect of possible interventions. The results from this monitoring are submitted on a yearly basis to the European Food Safety Authority (EFSA) since 2004. Prior to 2004, the data were submitted to the Commission. The data are analysed at EU level, and published as annual Community Zoonoses Reports. A review of these reports, which are available online from 2000 onwards, reveals that a considerable amount of antimicrobial susceptibility testing has been carried out. The data are presented for different bacterial species, i.e. *Salmonella*, *Campylobacter*, *E. coli* and *Enterococci*, and with reference to the samples' origin, i.e. different animal populations or different raw meats, mostly poultry, pigs and cattle. Despite the large volumes of data collected, the existence of discrepancies from country-to-country and between years in the data collected has reduced the opportunities to draw conclusions. Discrepancies include the extent of coverage of animal populations/food types, the bacteria and antimicrobials studied, and the methods and interpretation criteria applied. To address this problem, and since the entry into operation of the European Directive on the monitoring of zoonoses (Directive 2003/99/EC), a concentrated effort has been made to improve and standardise the collected data. To this end, detailed rules for monitoring AMR were first provided for *Salmonella* spp. in poultry and slaughter pigs in Commission Decision 2007/407/EC, and for *Campylobacter* spp. in broiler flocks in Commission Decision 2007/407/EC. The requirements on AMR monitoring have become more stringent and harmonised with regard to tested organisms, sample populations, methodology and interpretative criteria used. From 2014, Commission Implementing Decision 2013/652/EU, has extended existing monitoring to more animal and food sources, has introduced mandatory monitoring for commensal *E. coli* and for extended-spectrum beta-lactamases (ESBL)-, AmpC-, carbapenemase-producing *E. coli* and has provided detailed standardised rules for optional monitoring for faecal *enterococci* (see Table 4.1 for details).

As a general rule, the harmonised monitoring at European level aims to obtain data from 170 isolates per Member State per year for each combination of bacterial species and type of sample tested that year. Each combination should be tested at least every two years. Standardised dilution methods for susceptibility testing must be used. For each bacterial population, the legislation indicates the panel of antimicrobial substances to be included in AMR monitoring, the concentration ranges to be examined and the thresholds for interpretation of resistance.

Monitoring of AMR in animals and food is carried out in Ireland by the Central Veterinary Research Laboratory (CVRL) of the Department of Agriculture, Food and the Marine (DAFM), which acts as the National Reference Laboratory (NRL) for AMR in food, feed and animals in Ireland. Data on AMR from poultry *Salmonella* isolates are available since the early 1990s, *Campylobacter* monitoring began in 2008, and from 2011, monitoring was extended to commensal *E. coli* and *Enterococcus faecalis* and *Enterococcus faecium* in broilers.

In addition to those harmonised, active surveillance programmes of organisms isolated from healthy animals or food derived from those animals, useful data are also gathered through passive surveillance of AMR in bacteria implicated in animal disease. Antimicrobial susceptibility testing from veterinary clinical isolates is also carried out at diagnostic laboratories in Ireland, i.e. DAFM Regional Veterinary Laboratories (RVLs). Disc diffusion testing is carried out at the request of farmers and/or veterinarians to determine the susceptibility of animal pathogens isolated from samples from animals with clinical disease, e.g. mastitis, diarrhoea, septicaemia or pneumonia. Knowledge of the *in vitro* effect of the antimicrobial on bacteria is key when prescribing antimicrobials for diseased animals. Approximately 2,000 isolates are checked each year for this purpose from animal pathogens such as *Salmonella* spp., *E. coli*, *Staphylococcus* spp., *Streptococcus* spp., *Mannheimia hemolytica* and *Pasteurella multocida*. The DAFM laboratories, in discussions with Animal Health Ireland, are aiming to agree a process for the coordination and the harmonisation of procedures to facilitate collection and analysis of antimicrobial susceptibility data from mastitis cases.

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Other sources of AMR data relevant to the food chain include the annual reports for the Central Veterinary Research Laboratory, the Regional Veterinary Laboratories, the National *Salmonella*, Shigella and Listeria Reference Laboratory for Humans (NSSLRL) and the FSAI and scientific literature can be consulted.
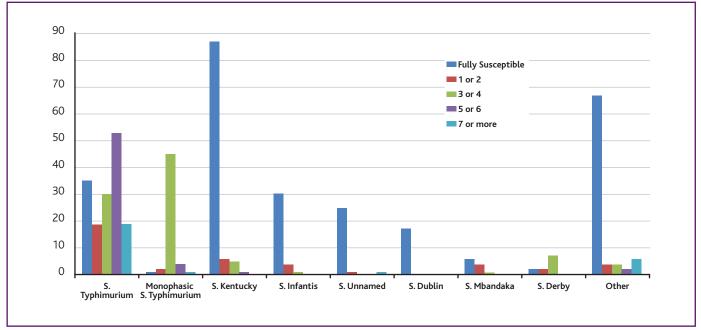
Table 4.1 Antimicrobial resistance data at different stages of the food chain in Ireland

	Mandatory EU monitoring (year harmonised monitoring started)	**Other antimicrobial resistance data**
Food-producing animals	- *Salmonella* isolates from farms of laying hens (2008), broilers (2009) and turkeys (2010) - *Campylobacter* from broilers caeca (2008) - Pigs and turkeys as part of 2007 and 2008 EU baseline studies - *Campylobacter jejuni* from turkeys caeca (2014) - *E. coli* and ESBL-, AmpC- or carbapenemase-*E. coli* from caecal samples of broilers, turkey, pigs and cattle (2014)	- CVRL data on commensal *E. coli* and ESBL-, AmpC-*E. coli*, on commensal *Enterococcus faecium* and faecalis in broilers, pigs and bovines and on *Campylobacter* spp. from broiler and pig and cattle caeca - RVL data on isolates from animal pathogens *Salmonella* spp., *E. coli*, *Staphylococcus* spp., *Streptococcus* spp., *Mannheimia hemolytica* and *Pasteurella multocida* causing enteritis, mastitis and pneumonia - Portions of the *Salmonella* spp. isolates submitted by commercial laboratories to CVRL are tested for antimicrobial susceptibility and results reported to EFSA and incorporated in the annual CVRL reports. Approximately 50-100 isolates each year
Food of animal origin	- Pig carcasses in 2007 only as part of a baseline study - *Salmonella* from carcasses of broilers, turkeys, pigs, cattle (2014) - ESBL-, AmpC- or carbapenemase-*E. coli* from raw broiler, bovine and pig meat at retail (2015)	- *Salmonella* spp., *Campylobacter* spp., vero toxigenic *E. coli* (VTEC) and *Listeria monocytogenes* from DAFM official testing or from baseline studies - A portion of the *Salmonella* spp. isolates submitted by commercial laboratories to CVRL are tested for susceptibility to antimicrobial agents and results reported to EFSA and incorporated in the annual CVRL reports - Some research papers on *Salmonella* spp. in food in Ireland, e.g. on pigmeat, poultry meat and milk, contain data on AMR - 2014 DAFM laboratories study of *E. coli* AMR from meat products

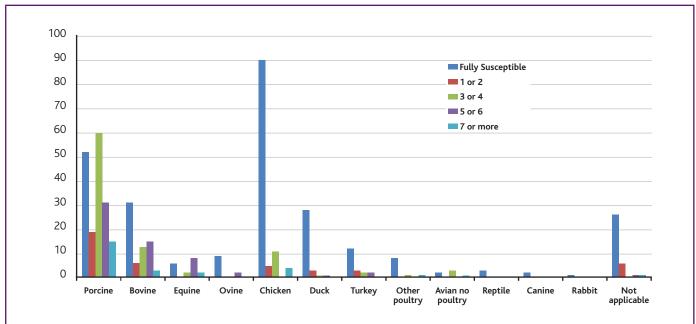|	Mandatory EU monitoring (year harmonised monitoring started)	Other antimicrobial resistance data
Food of non-animal origin	None	*Salmonella* spp. strains that are isolated by commercial laboratories (rare occurrence) are tested by CVRL. Approximately 0-10 each year. Occasional *Salmonella* spp. isolates from the Official Food and Water Microbiology laboratories may be submitted to the NSSLRL for human pathogens.
Imported food	None	Some of the *Salmonella* spp. strains received from commercial laboratories and tested for antimicrobial susceptibility may originate from imported foods, however this information is unknown.
Water and environment	None	*Salmonella* strains that are isolated by commercial laboratories (rare occurrence) are tested by CVRL. Approximately 0-10 each year.

In Ireland, the situation regarding AMR in meat-producing animals and food of animal origin is broadly comparable with that of most other European countries, with resistance to antimicrobials commonly found among *Salmonella* spp., *Campylobacter* spp. and the indicator *E. coli* and *Enterococci* from animals and food. More detail is available in the EFSA Community Zoonoses Reports.

Among *Salmonella* strains, a strong association exists between the AMR pattern and the serovar/phage type (Figure 4.1). For example, a high level of AMR is associated with *S.* Typhimurium, a serovar frequently isolated in Ireland, mainly from samples from the pig production sector. More specifically, within *S.* Typhimurium, the association of phage type DT104 with pentad-resistance to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracyclines is well known and prevalent. In more recent years, high prevalence was reported for monophasic *S.* Typhimurium phage type DT193 with the combination of resistance to ampicillin, streptomycin, sulphonamides and tetracyclines. In the group of *Salmonella* serovars considered of public health importance, in addition to *S.* Typhimurium and monophasic *S.* Typhimurium, the main serotypes are *S.* Enteritidis (only infrequently isolated from Irish animals and food samples), as well as *S.* Hadar, *S.* Virchow and *S.* Infantis. The level of AMR in isolates of these serovars is in general, medium to high, and they tend to exhibit higher levels of resistance to quinolones than isolates belonging to other serotypes.

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Figure 4.1. *Salmonella* **isolates of different serotype and number of antimicrobials to which they are resistant** (National Reference Laboratory Antimicrobial Resistance Food Feed and Animal Health, 2011)

When considered by antimicrobial classes, resistance among *Salmonella* isolates is most common against sulphonamides, tetracyclines, streptomycin and ampicillin (approx. 30% of all isolates). In addition to variations in resistance related to serovar, levels of resistance are also associated with the animal species from which the isolates originated. This is considered to be related at least in part to differences in the patterns of use of antimicrobial agents in these animal species. Multi-resistant *Salmonella* spp. occur more frequently in the pig sector than in poultry or cattle and resistance is most uncommon in isolates from sheep or from non-farm animals (Figure 4.2). The effect of antimicrobials may also be relevant to the high level of resistance sometimes observed in isolates recovered from animals treated for infection, e.g. *Salmonella* Typhimurium strains from cattle and horses with resistance to more than eight antibiotic classes have been observed (National Reference Laboratory Antimicrobial Resistance Food Feed and Animal Health, 2011).

Figure 4.2. *Salmonella* **strains of different animal origin and number of antimicrobials to which they are resistant** (National Reference Laboratory Antimicrobial Resistance Food Feed and Animal Health, 2011)
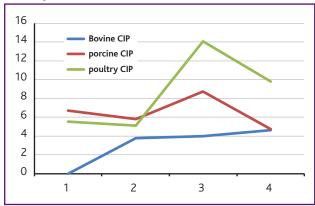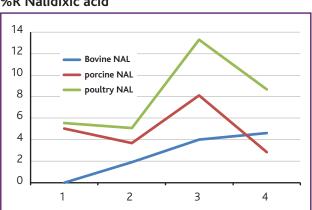

Of particular interest nowadays is resistance to those agents defined as critically important antimicrobials in human medicine (see Chapter 1), including fluoroquinolones, third and fourth generation cephalosporins, carbapenems and macrolides. Among *Salmonella* isolates of animal origin, the overall prevalence of resistance towards ciprofloxacin and the related, though less potent agent, nalidixic acid is low (5% of isolates), although the percentage is higher in isolates from poultry. A trend towards increasing fluoroquinolone resistance in poultry isolates has been observed over recent years (Figure 4.3). Resistance to third and fourth generation cephalosporins in *Salmonella* is also higher among poultry isolates. Occurrence of strains harbouring ESBL has been described in Ireland in strains from food and animals and, although uncommon, it has intermittently been associated with *S.* Kentucky isolates from broilers and chicken. These included a CMY-2 plasmid-mediated AmpC producers and SHV-12 ESBL-producers.

Figure 4.3. Trends in resistance to fluoroquinolones and quinolones in *Salmonella* isolates of bovine, porcine and poultry origin from 2008 (point 1) to 2011 (point 4) (National Reference Laboratory Antimicrobial Resistance Food Feed and Animal Health, 2011)

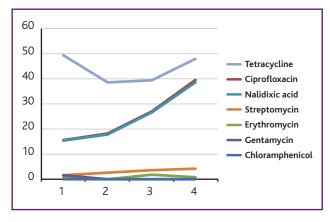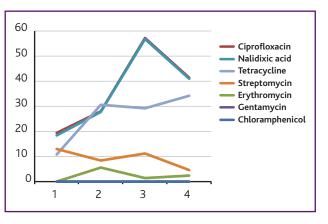**%R Ciprofloxacin**

%R Nalidixic acid

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Approximately 90% of porcine and 60% of poultry *Campylobacter* isolates tested are resistant to one or more antimicrobial agents, while the percentage is less than 20% among bovine isolates. Most commonly observed resistance is towards ciprofloxacin, nalidixic acid, tetracycline and streptomycin. As with *Salmonella* isolates from poultry, the levels of resistance to ciprofloxacin and nalidixic acid in *Campylobacter* isolates from poultry have increased in recent years (Figure 4.4).

Figure 4.4. Trends on resistance levels to tested antimicrobials from 2008 (point 1) to 2011 (point 4) in *Campylobacter jejuni* (left chart) and *Campylobacter coli* (right chart) isolates from poultry (National Reference Laboratory Antimicrobial Resistance Food Feed and Animal Health, 2011)

Data from the NRL Antimicrobial Resistance 2011 Annual Report shows that there are high levels of AMR in commensal *E. coli* and *Enterococci* isolated from broilers. Among *E. coli* isolates from broilers, the AMR levels are very high, with approximately 50% resistant to ampicillin, sulphonamides and tetracycline, 40% to streptomycin and trimethoprim, and more than 30% to ciprofloxacin or nalidixic acid. In addition, ESBL *E. coli* have been isolated from nearly two-thirds of broiler flocks examined. Among *Enterococci* spp. from broilers, the level of resistance is high for tetracyclines, erythromycin and streptomycin. Interestingly, resistance to vancomycin is uncommon.

A study of AMR patterns of *E. coli* isolated from various meat products in Ireland was conducted by DAFM Laboratories in 2013-2014 (Power, 2014). A total of 184 *E. coli* isolates obtained from raw meat samples were investigated. Resistance to ampicillin, streptomycin, tetracyclines and sulfamethoxazole was common in isolates from raw meat (chicken, turkey, bovine and porcine). Multi-drug resistance to three or more classes of antimicrobials was commonly detected but co-resistance to the fluoroquinolone, ciprofloxacin, and third generation cephalosporins was low. Chicken and turkey meat harboured the highest levels of antimicrobial-resistant *E. coli*, and the highest levels of resistance to clinically important antibiotics such as ciprofloxacin. Extended-spectrum beta-lactamase and AmpC-producing *E. coli* were detected in meat products at a low rate, with the highest levels detected in chicken and turkey meats. Although the limited number of samples from imported products did not permit meaningful comparison with domestic meats, the most highly resistant isolate recovered during the research was from imported spiced turkey. This isolate was resistant to 14 different antimicrobials.

Information on AMR on food of non-animal origin, including water, is very limited and primarily from research. Antimicrobial-resistant *E. coli*, including third generation cephalosporin-resistant *E. coli*, have been recovered from water in Ireland, including from rural drinking water sources (Cormican *et al.*, 2012). There is no specific monitoring of AMR in imported foods or water. Isolates submitted to the CVRL by commercial laboratories do not contain specific information regarding country of origin. Therefore, there is no current system to allow comparison of AMR between imported and domestic food.

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CHAPTER 5. USE OF VETERINARY ANTIMICROBIAL AGENTS IN IRELAND

5.1   Introduction

In veterinary medicine, antimicrobial agents are used both for the treatment of individual animals and also for the medication of groups of animals, if required. In Ireland, medication of groups of animals is carried out most commonly in intensively reared farm animals such as pigs, poultry and farmed fish. Antimicrobials may be used for therapy, metaphylaxis or prophylaxis. EPRUMA, (European Platform for Responsible Use of Medicines in Animals, 2013) defines therapeutic treatment as the treatment of animals following diagnosis of disease. Metaphylaxis is defined as medication of groups of animals when disease has been diagnosed in some members of the group, with the aim of treating the clinically affected animals, while preventing spread of disease to unaffected or sub-clinically affected animals. Finally, prophylaxis is defined as medication of animals before clinical signs of disease in order to prevent the occurrence of disease.

5.2   Regulatory Framework for Antimicrobial Use in Veterinary Practice

Antimicrobial agents are animal remedies that are administered by veterinarians and farmers to animals. Knowledge of the regulatory framework within which animal remedies are used is important in order to understand the context of their use and is outlined in this section.

The use of antimicrobial agents in food animals is governed by various pieces of European and Irish legislation relating to the production, distribution, supply and administration of medicine to food animals. At EU level, the primary legislation is set out in Directive 2011/82/EC, and at national level the primary legislation is the Animal Remedies Act No. 23 of 1993. The detailed provisions are set out nationally (S.I. No. 786 of 2007). In addition to this medicine framework, other relevant legislative frameworks include those pertaining to residues, food safety, animal health and animal by-products.

In very general terms, the regulatory framework around animal remedies is designed around the following concepts:

· Only medicines of adequate quality, safety and efficacy are administered to animals

· Administration is restricted to circumstances where there is sufficient benefit to recipient animals

· Consumers of products derived from the recipient animals are protected from risks to their health related to the products

The approach to ensuring the safety quality and efficacy is one of requiring the authorisation of all animal remedies by a competent authority, following demonstration of the appropriate characteristics by the pharmaceutical company intent on placing the product on the market. In Ireland, this responsibility rests with the Health Products Regulatory Authority (HPRA). Only products which have been allocated a Veterinary Product Authorisation (VPA) may be sold or administered to animals. There is an exception known as the 'cascade'. This is an exceptional mechanism provided for in EU and national legislation[2] for situations where there is no authorised product to treat a particular condition in an animal. In such circumstances, a veterinary practitioner may use a human medicine authorised for the Irish market by HPRA or an animal remedy authorised in another Member State of the EU. However, in the case of the 'cascade' there is a distinction between food and non-food animals. In the case of food animals, only substances with a Maximum Residue Limit (MRL) may be used and minimum withdrawal periods apply.

[2]   Articles 10 & 11 (Directive 2001/82/EC) (as amended) which is given effect in Irish legislation in Regulation 18 of the European Communities (Animal Remedies) (No.2) Regulations, 2007 (S.I. No. 786 of 2007)

The VPA of each animal remedy categorises remedies to designate the allowable supply route for that formulation:

- VSO. Veterinary Surgeon-Only. These may only be dispensed and administered by a veterinary practitioner

- POM. Prescription Only Medicine. These remedies may only be dispensed according to a prescription by a veterinary surgeon. Their dispensing and administration may be done by non-veterinarians in accordance with that veterinary prescription

- Pharmacy only (PS) and Licensed Merchant (LM) products may only be dispensed by a pharmacy or by a licensed merchant respectively

The VPA for antimicrobial animal remedies generally designates such products as POM, thereby requiring a veterinary prescription prior to administration. The regulatory framework requires such prescriptions to be issued by veterinarians only for animals under their care. This concept of 'under their care' obviously applies to an individual animal that has been examined. However, modern animal husbandry systems can involve the intensive production of large numbers of animals with health-care considered at a herd/flock level. The regulations therefore allow for a broader concept of groups of animals being regarded as under the care of the prescribing veterinarian when the herd/flock is subject to a general health programme under the stewardship of that veterinarian. The mass medication of large numbers of individual animals, e.g. through medicated feed premixes, may arise through prescriptions within this health programme care concept. Whilst such herd health programmes involve substantial reliance on productivity records, the legislation requires recent and frequent visits to ensure appropriate prescribing in such scenarios, and there exists a specific obligation for a visit to the herd within the 12 months preceding a prescription.

However, in the case of antimicrobial animal remedies formulated for infusion through the teat of lactating animals, Irish legislation (Schedule 8 of the Animal Remedies legislation) creates a specific provision. Intramammary antimicrobials may be prescribed for bovine animals in a manner outside of the generally applicable concept of an animal under the care of a veterinary practitioner, provided those animals are subject to a programme designed to prevent and treat mastitis. Mastitis is the inflammation of the mammary gland, generally arising from infection. It has clinical and subclinical manifestations and is one of the more prevalent infectious disease problems encountered in the farming of lactating animals. Intramammary formulations are frequently used in the management of bovine mastitis. The practice of 'dry cow therapy' involves the intramammary administration of antimicrobial formulations designed to have a sustained effect to treating and prevent infections during the dry (non-lactating late-pregnancy) period.

A key part of the regulatory basis for administering animal remedies to food animals is the management of risks that might arise to consumers through the consumption of the food products harvested from those animals, e.g. meat, milk, eggs or honey. The decline of concentration of the remedy within animal tissues after administration is assessed and a withdrawal period (the minimum duration from administration until harvesting of food from an animal) is established for all remedies authorised for use in food animals. Distributors, suppliers, prescribers, and administrators of animal remedies are required to maintain appropriate records, and the on-farm animal remedy register should support compliance by farmers in deciding when to allow food products enter the food chain. However, in the context of the current report, it should be noted that the assessment of the appropriate withdrawal period for animal remedies is assessed solely on the basis of the direct toxicological effects of the residual chemical hazard that might be consumed. The potential of antimicrobial administration to increase the number of antimicrobial-resistant microbes in that animal and for this to persist after elimination of the antimicrobial agent is not considered.

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5.3   Training as it Relates to Antimicrobial Use and Antimicrobial Resistance

As veterinarians and farmers play a key role in the administration of antimicrobial agents to animals, this section briefly outlines aspects of training relevant to this function.

5.3.1   Veterinary training

The training requirements for veterinarians are set out in EU legislation (Directive 2005/36/EC and Directive 2013/55/EC). At a general level, the training requirements include animal health, animal diseases, therapies, and ramifications for public health. The regulations set out core areas of competence which veterinary curricula should impart including:-'the knowledge, skills and competences required for the responsible and sensible use of veterinary medicinal products, in order to treat the animals and to ensure the safety of the food chain and the protection of the environment.'

Compliance with training requirements in EU veterinary training establishments is assessed at an EU level (www. eaeve.org). The Irish Veterinary Practice Act requires all veterinary practitioners in Ireland to be registered with the Veterinary Council of Ireland (VCI). Such registration may only take place on the basis of the VCI acceptance of the training and qualifications of the practitioner.

AMR has veterinary relevance both in terms of efficacy of therapy within veterinary clinical situations, and also the wider concept of foodborne AMR. The relevance of training in the foodborne AMR concept has been highlighted in an overview of veterinary curricular requirements by the World Animal Health Organization (OIE) (Fanning *et al.*, 2009).

5.3.2   Agricultural training as it relates to antimicrobial use and antimicrobial resistance

Key principles related to animal feed regulations and livestock medicines and remedies are included in the curriculum for the Level 5 Certificate on Food Assurance in Agriculture offered by Teagasc. Level 5 skills training includes dosing and injecting and associated best farm practice and records required. In addition, livestock production modules at level 5 and 6 cover herd health and husbandry.

5.4   Available Data on Antimicrobial Use in Food animals in Ireland

Data on antimicrobial use in animals in Ireland are limited. With respect to food-producing animals in Ireland, there is a legal obligation that all medicines administered are recorded on-farm however, there is neither central return nor collation of such data. Some indicative information can be obtained by examining antimicrobial sales data. The primary source of antimicrobial sales data is contained in figures collated and published by the HPRA for the last five years (2009 to 2013). These data are collated by the HPRA for the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) programme. These assessments are based purely on data supplied by manufacturers, distributors and wholesalers, so are not point-of-use data indicating the species to which they were actually administered.

An additional complication in relation to these data is that national and EU legislation recognise the need for veterinary practitioners, in exceptional circumstances, to be able to use certain medicines off-label, i.e. not strictly in accordance with the conditions of authorisation of the medicine. This is commonly referred to as use under the 'cascade' provisions of the legislation, and applies exclusively to veterinary practitioners.

Sales data are only indicative of use in animals, as in cases where the product is licensed for use in a number of animal species; the proportion of sales for use in each species is not recorded. In addition, there are other sources of potential error whereby some antimicrobial sales may be missed or data may be inaccurate. For example, some of the feed used in the pig industry may be imported from another country and these sales are probably recorded in their data rather than in Irish figures. Human drugs which might be prescribed by veterinarians under the 'cascade' are also not included in the sales data collected. Data on use of antimicrobials in fish are not readily visible from sales data because the products used in fish are often administered via the 'cascade' and not therefore, labelled or sold for fish.

5.5   The Sales Data

The total tonnage of antimicrobials sold for veterinary use in Ireland in 2013 was 100 tonnes, which was an increase on the figure of 97.4 tonnes sold in 2012 and of 85.2 tonnes reported for 2011. Figures 5.1 and 5.2, taken from the HPRA report for 2013, show total sales broken down according to class of antimicrobial and pharmaceutical form, respectively (IMB, 2013).
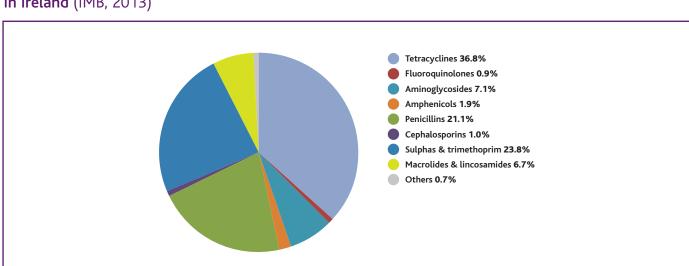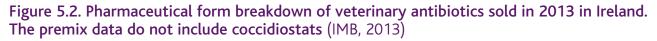
Figure 5.1. Distribution of sales (based on tonnes sold) of veterinary antibiotics supplied in 2013 in Ireland (IMB, 2013)

- Tetracyclines **36.8%**
- Fluoroquinolones **0.9%**
- Aminoglycosides **7.1%**
- Amphenicols **1.9%**
- Penicillins **21.1%**
- Cephalosporins **1.0%**
- Sulphas & trimethoprim **23.8%**
- Macrolides & lincosamides **6.7%**
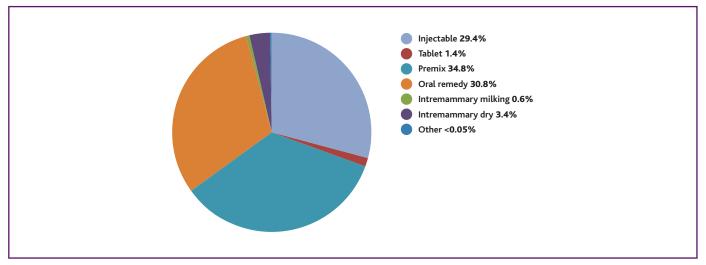- Others **0.7%**

Figure 5.1 shows that the bulk of sales were of the 'older antibiotics,' which have been used in human and veterinary medicine for decades: penicillins, tetracyclines, sulphonamides and aminoglycosides. However, these data must be interpreted with caution as they are not necessarily reflective of the number of doses received by animals. The size of the daily dose of an antimicrobial agent by weight is generally greater for less potent antimicrobial agents and may be greater for those that need to be given multiple times per day rather that once per day. Many older antimicrobial agents are less potent gram for gram. Assessing use in simple terms of kg sold/prescribed can therefore be misleading in terms of the number of doses/treatments given. For example, a kg of a fluoroquinolone, e.g. ciprofloxacin, may have the antimicrobial activity equivalent to many kg of the quinolone nalidixic acid. The proportion of each antimicrobial class sold has not greatly changed between 2009 and 2013, apart from the macrolides and tetracyclines, which have increased and the sulphonamides which have decreased as a proportion of the whole. However, unpublished data from the HPRA in Table 5.1 also shows an increasing trend in recent years in sales of the fluoroquinolones and third and fourth generation cephalosporins, which are listed as critically important antimicrobial agents in human medicine.

In food animals, fluoroquinolones are licensed for the treatment of respiratory and enteric conditions in cattle, pigs and poultry. However, anecdotally their use in poultry may be decreasing in response to the demands of the large supermarket chains. Third and fourth generation cephalosporins are licensed for use in the treatment of respiratory conditions in cattle and pigs and for treatment of intramammary infections, foot infections and metritis in cattle. Macrolides such as tylosin and tilmicosin are licensed for use in pigs, poultry and cattle for treatment of a number of infections, including respiratory and enteric conditions in all three species and mastitis in cattle.

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Table 5.1 Sales of antimicrobials according to class from 2009 to 2012 (tonnes)
(HPRA unpublished data)

Antibiotic group	Tonnes sold by year			
	2009	2010	2011	2012
Tetracyclines	32	33.2	30.4	37.2
Penicillins	19.9	19.9	21.3	22.4
Sulphonamides	23.9	22.4	19	20
Macrolides	1.87	7.96	4.56	6.65
Aminoglycosides	7.24	7.5	7.6	8.4
Amphenicols	1.65	1.27	1.42	1.99
Fluoroquinolones	0.66	0.67	0.71	0.99
Cephalosporins	0.63	0.73	0.93	0.88
Total	**91.1**	**96.7**	**88.5**	**101.2**

Figure 5.2. Pharmaceutical form breakdown of veterinary antibiotics sold in 2013 in Ireland. The premix data do not include coccidiostats (IMB, 2013)

Legend:
- Injectable 29.4%
- Tablet 1.4%
- Premix 34.8%
- Oral remedy 30.8%
- Intremammary milking 0.6%
- Intremammary dry 3.4%
- Other <0.05%

A major limitation of these data collected by ESVAC is the fact that they are based on total antimicrobial sales per country and these are not broken down per animal species. In order to overcome this difficulty, the European Medicines Agency (EMA) has introduced the term 'population correction unit' (PCU). EMA defines the PCU as 'the estimated weight at treatment of livestock and of slaughtered animals in the corresponding year, taking into account the import and export of animals for fattening or slaughter in another Member State'. A PCU for all livestock produced in a country can be calculated and also individual PCUs for each animal species. However, the data need careful interpretation. For example, figures taken from the most recent EMA report (EMA, 2014) which contains 2012 data expressed as mg/kg of animal biomass, suggest at first glance that antimicrobial use in animal production in Ireland is below the European average. The Irish figure is 58 mg/kg compared to the EU average of 144 mg/kg (range 3.8 - 396.5 mg/kg) (Figure 5.3, taken from EMA, 2014). However, it is worth noting that Ireland has proportionally more cattle than many other countries (Fig 4, taken from EMA, 2014) and in addition, much of our beef and milk production are produced at grass and utilise low levels of antimicrobials. Thus, comparison of antimicrobial use in mg/PCU does not give a good representation of antimicrobial use in the different species in countries with different proportions of animal species and different production systems.
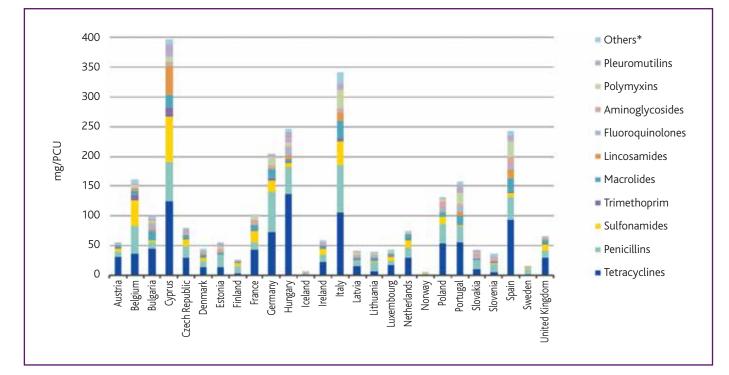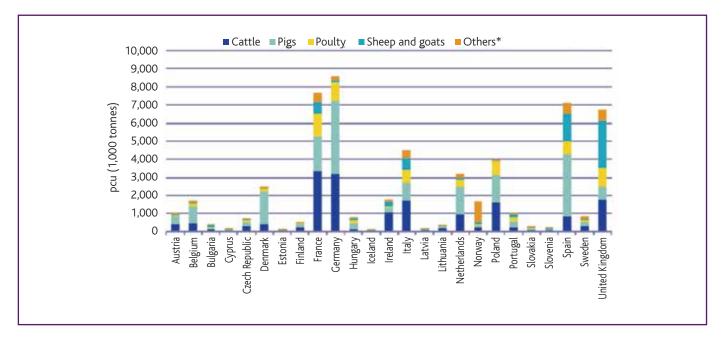
Figure 5.3. Sales for food-producing species, including horses, in mg/PCU, of the various veterinary antimicrobial classes, by country, for 25 countries in 2012 (EMA, 2014)

Figure 5.4. PCU (in 1,000 tonnes) of the various food-producing animal species, including horses, by country for 2012 (EMA, 2014)

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5.5.1   Sales and usage practices in pigs

Antimicrobial use in intensively farmed animals is usually greater than in other production systems and thus sales of antimicrobials in the pig and poultry industries are examined in some detail in this report.

In order to evaluate antimicrobial use in Ireland broken down according to animal species, in the absence of accurate data on antimicrobial sales, it is necessary to make various assumptions. Table 5.2 shows how use in the pig industry can be estimated, depending on which assumptions are made. The pig industry is taken as an example of an intensive meat production industry. The sales data are taken from the HPRA data for 2011 and the pig PCU is taken from the third ESVAC report (EMA, 2013). The kg of pig meat produced in 2011 was taken from the Central Statistics Office website (Central Statistics Office, 2012).

Calculation A uses figures provided by the marketing authorisation holders to the HPRA in periodic safety update reports. In these reports, the marketing authorisation holders estimate the proportion of sales that is used in each target species, where a product is licensed for use in a number of different species. Based on the 2011 data, there were 47 authorised oral antimicrobial product presentations (premix, oral powder and solution) sold for use in pigs. Of these, 20 were authorised for use in several target species, generally pigs and poultry. It is unknown how the marketing authorisation holders determine the proportion of sales in each species. Thus, in order to account for uncertainty in target species use, a conservative second approach was used (Calculation B). Where a product was authorised for use in several species, it was assumed that 100% of the product was used in pigs. Calculation A gives a figure of 85.7 mg/PCU for sales of oral formulations, whereas the figure for calculation B is 135.2 mg /PCU. Calculation B represents what might be termed a 'worst case scenario' and the true figure probably lies somewhere between the two.

Table 5.2 Estimated sales of oral antimicrobial agents in the pig industry in Ireland for 2011, based on different assumptions

Unit	
Total antibiotic sales (tonnes active ingredient)	87
Total premix, oral powder and solution (% of total)	64
Total premix, oral powder and solution (tonnes)	55.7
Pig PCU ('000 tonne)	265
Estimated kg pig meat produced in 2011 ('000 tonnes)	235
A. Calculations using estimations of marketing authorisation holder	
Estimated total premix, oral powder and solution used in pigs based on estimated distribution (tonnes)	22.7
Sales oral formulations/pig PCU only (mg/PCU)	85.7
Sales oral formulations/kg pig meat produced	96.6
B. Calculations assuming 100% use in pigs where authorised for pigs	
Estimated total premix, oral powder and solution used in pigs assuming 100% use (tonnes)	35.83
Sales oral formulations/pig PCU only (mg/PCU)	135.2
Sales oral formulations/kg pig meat produced	152.5

A system of recording antimicrobial use and resistance has been in place in Denmark for a number of years (see Chapter 6). A figure of 40 mg of antimicrobial agent/kg pig meat produced was given in DANMAP for 2011(DANMAP, 2011). This includes all antimicrobial usage, both oral and injectable formulations and is considerably lower than either of the figures estimated in Table 5.2 for sales of oral formulations/kg pig meat produced in Ireland [96.6 mg/kg (Calculation A) or 152.5 mg/kg (Calculation B)]. However, estimated antimicrobial use in pigs in many other European countries is similar to, or greater than, use in Ireland.

Data from a University College, Dublin (UCD) study (Gibbons, 2011) support the finding of high antimicrobial use in the pig industry in Ireland. At the time farm visits were carried out, only eight farms of a total of 39 were recorded as not using antimicrobial agents in pig feed, with 14 farms medicating piglet, link and weaner feed. Peak use of antimicrobials occurred at weaning, which is in accordance with findings in other countries. Pigs in most intensive systems are weaned at three to four weeks of age and are moved to new housing, with pigs from several litters being mixed together, usually according to size and weight. The stress associated with removal from the dam and opportunity for transmission of infection associated with mixing pigs at this time means that the risk of disease is particularly high at weaning. Thus prophylactic medication for prevention of disease, including nervous, enteric and respiratory infections, is common in many countries, including Ireland. Few farms medicate feed of finishing pigs and only two of 39 farms medicated finishing feed in the UCD study (Gibbons, 2011). There are challenges for the pig industry in Ireland in relation to antimicrobial use, one of these being the feeding systems in place on many farms. Many systems do not allow small numbers of pigs to be medicated for short periods of time and there are problems with excessive duration of treatment and carryover of medication to groups of animals which do not require medication (Healy, 2013). Introduction of systems which facilitate medication of water might help to address some of these problems, but there are associated costs for an industry with already tight profit margins.

5.5.2   Sales of antimicrobials in poultry

Antimicrobial sales in poultry in Ireland can be estimated in a similar manner to that employed for pigs and figures are given in Table 5.3. Antimicrobials are frequently used in day-old birds to prevent and treat yolk-sac infection and again in older birds around 20 days of age to avert the effects of enteric disease. Medication is usually through drinking water. However, anecdotal evidence suggests that some farms with optimum management systems and tight biosecurity can rear birds with minimal or no antimicrobial use.

Table 5.3 Estimated sales of oral antimicrobial agents in the poultry industry in Ireland for 2011, based on different assumptions

Unit	
Total antibiotic sales (tonnes active ingredient)	87
Total premix, oral powder and solution (% of total)	64
Total premix, oral powder and solution (tonnes)	55.7
Poultry PCU ('000 tonne)	79
Estimated kg poultry meat produced in 2011 ('000 tonnes)	131
A. Calculations using estimations of marketing authorisation holder	
Estimated total premix, oral powder and solution used in poultry based on estimated distribution (tonnes)	7.5
Sales oral formulations / poultry PCU only (mg/PCU)	94.9
Sales oral formulations / kg poultry meat produced	57.3
B. Calculations assuming 100% use in poultry where authorised for poultry	
Estimated total premix, oral powder and solution used in poultry assuming 100% use (tonnes)	11.11
Sales oral formulations / poultry PCU only (mg/PCU)	140.6
Sales oral formulations / kg poultry meat produced	84.8

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Direct comparison with Danish figures is not possible because of different units of measurement and separation of figures for different types of poultry such as broilers, turkeys and game birds. Graphical representation of usage in the DANMAP report of 2011 shows that use of antimicrobials in broiler production in Denmark is low, only 1-2mg/kg meat produced; use in turkeys is higher, approximately 27mg/kg meat produced (DANMAP, 2011). These figures suggest that use in Ireland in the poultry sector is considerably higher than in Denmark although information from specialist poultry practitioners suggests that use in broiler production is also low in Ireland. Practitioners also state that use of vaccination is increasing in the sector.

5.5.3   Antimicrobial sales and usage practices in cattle

Figures for oral antimicrobial sales in cattle can be estimated from the HPRA data shown in Tables 5.2 and 5.3. Based on estimations from the marketing authorisation holders, 22.7 and 7.5 tonnes of oral formulations were used in pigs and poultry respectively, in 2011. This implies that 25.5 tonnes of oral preparations were used in cattle, to make up a total of 55.7 tonnes of product sold. In the cattle sector, oral antimicrobials are used primarily in pre-ruminant calves, thus it is likely that much of the 25.5 tonnes was used in the 2,085,500 calves born in Ireland in 2011 (DAFM, 2011).

Data on sales of intramammary antimicrobial agents in Ireland between 2003 and 2010 and estimated use in lactating and dry cows in this period have been published by More *et al*. (2012). Dry cow therapy is a risk management tool in accordance with adopted *Codex Alimentarius Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (Codex Alimentarius Commission, 2011) and other Codex codes however, More *et al*., (2012) estimate that almost 93% of dry cows in Ireland are receiving treatment. The International Dairy Federation expressed the view that there was no apparent progression of AMR in mastitis pathogens after four decades of antimicrobial drug use in dairy cows (International Dairy Federation, 2013).

Approximately 500kg of lactating cow antimicrobial agents were sold in 2010 to treat an estimated 54 cases of mastitis per 100 cow-years at risk. These data suggest a high rate of antimicrobial use during lactation, most likely in response to clinical cases of mastitis. However, the efficacy of mastitis therapy for chronic *Staphylococcus aureus* infection during lactation is extremely low (Pyörälä, 2009), leading to very low cure rates following treatment. Therefore, there may be an over-reliance on antimicrobial agents in the dairy industry in Ireland for this application.

As with other species, there are few data available on antimicrobial use, as opposed to sales, in cattle in Ireland. Gibbons *et al*., (2014) examined antimicrobial use in 14 spring calving dairy herds and these data are shown in Table 5.4. In this case, usage is calculated as the number of defined animal daily doses for a 50kg animal (ADD50) which is a more accurate measure of usage than mg/PCU. Consistent with overall sales data in Ireland, it can be seen that greatest usage is of the older antimicrobials, including the penicillins, aminoglycosides (streptomycin, always administered as penicillin/streptomycin combination) and tetracyclines. The proportion of ADD50 comprising of antimicrobials designated as critically important in human medicine is low - fluoroquinolones 4%, third generation cephalosporins 1.5% and macrolides 5%.

Table 5.4 Number of defined animal daily doses for 50kg animal (ADD50) of each antimicrobial supplied on 14 farms by three month period (Gibbons *et al.*, 2014)

Antibiotic	Q1[a]	Q2[a]	Q3[a]	Q4[a]	Total No. of ADD50 prescribed	No. of farms drug prescribed on
Amoxicillin/ clavulanate	5	9	9	555	578	11
Penicillins & Aminopenicillins	940	724	1,882	5,044	8,590	14
Ceftiofur	200	0	100	100	400	1
Fluoroquinolones	148	205	145	649	1,147	10
Florfenicol	0	0	0	23	23	2
Gentamicin	0	22	16	496	534	6
Streptomycin	640	564	1,422	3,786	6,412	14
Other Aminoglycosides[b]	0	48	60	313	421	5
Sulphonamide[c]	176	203	160	384	923	9
Tetracyclines	50	660	770	4,113	5,593	11
Macrolides	82	88	110	1,135	1,415	10
Total	**2,241**	**2,523**	**4,674**	**16,598**	**26,036**	

[a] Q1 – May 2007-July 2007; Q2 – Aug 2007-Oct 2007; Q3 – Nov 2007-Jan 2008; Q4 – Feb 2008-Apr 2008

[b] Framomycin and neomycin

[c] Includes trimethoprim/sulphonamide combinations

A seasonal trend can be observed, as might be expected in spring calving herds, with the highest proportion of use occurring between February and April, when cows are calving and there are a high number of young animals on farms.

5.5.4   Antimicrobial practices in aquaculture production

Aquaculture has been considered important in assessing the risk of AMR in the food chain (Cabello, 2006; FAO/OIE/ WHO, 2006; Cabello, 2013). However, differing aquaculture practices exist throughout the world and the extent to which these risks have been truly characterised is minimal (Park *et al.*, 2012),

Ireland has developed a substantial aquaculture industry. Approximately half of the farmed biomass in Irish waters comprises bivalve molluscs, notably mussels both rope-grown and bottom-grown, as well as oysters, which are normally grown on intertidal foreshore trestles. Other minority species farmed in Ireland include abalone. These animals graze on naturally-occurring phytoplankton and their husbandry does not incorporate any aspect of feeding nor treatment, and antimicrobial use does not arise. The other component of aquaculture is the farmed finfish industry, comprising mostly salmon farmed in surface-suspended inshore cages. Other minor farmed finfish in Ireland include sea-trout, char and turbot. Inland freshwater farming of brown trout also takes place in several sites in Irish rivers and lakes.

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Farmed finfish do receive animal remedies, notably including anti-parasitic formulations to deal with sea-lice and antimicrobial formulations to address bacterial infections.

Administration of medication to farmed finfish may involve parenteral injection (for vaccines) or medication of feed or immersion in medicated water using a 'well boat'. As a minor usage species, there is a paucity of licensed formulations for farmed finfish in general. Antimicrobials may be administered, based upon the 'cascade' system, whereby formulations licensed in other food animals are prescribed for use in fish. Farmed finfish are food animals under EU and Irish legislation and are subject to the same obligations as terrestrial food animals, including animal remedy controls, and the obligation to maintain treatment records on-farm. However, the lack of granularity in the available data on antimicrobial sales means that there is little information available regarding antimicrobial use in this sector.

Vaccination protocols are in place to minimise the prevalence of key bacterial diseases, e.g. furunculosis, a bacterial disease of salmon and trout, and hence minimise antimicrobial usage. Ireland's farmed salmon production is currently dominated by one key commercial operator, and is almost exclusively registered organic production.

5.5.5   Future developments

Antimicrobial sales data are not equivalent to usage data and do not provide a sound basis for evaluating usage or for risk analysis of resistance development. Sales data which are not broken down according to species are even less useful for evaluating veterinary prescribing practices and usage practices in animals. In order to address these problems, ESVAC proposes that data are provided which *"will be the prescribed or estimated amounts used, in weight of active ingredient, by country and year for each product (name and pharmaceutical form or administered route) per defined animal species and weight group/production type"* (European Medicines Agency, 2013a). It is further suggested that the unit of measurement should be 'defined daily dose animals' which is similar to the 'defined daily dose' used to measure antimicrobial use in humans, thus enabling analysis of human and animal usage data together. A pilot programme is currently underway in selected EU Member States in which data on antimicrobial use in pigs are being collected.

5.6   Disposal of Unused Antimicrobial Agents

Statutory Instrument No.786 of 2007 (Animal Remedies Regulations) stipulates that all surplus or waste antimicrobial products must be disposed of by return to the person from whom the farmer purchased the product. Veterinarians may charge for providing such a service. In 2014, there was a pilot initiative coordinated by the Environmental Protection Agency, in collaboration with Teagasc, the Department of Agriculture, Food and the Marine, and local authorities, in which farmers could bring out-of-date or unused medicines to a collection centre for disposal. It was part of a general farm hazardous waste collection scheme, which was repeated in 2014 and again in 2015. The relevant bodies are working to establish a long term national collection scheme for farm hazardous waste. At present, we do not have good data on how medicines are disposed of but some sources indicate that disposal in slurry may occur.

5.7   Monitoring of Antimicrobial Residues in Foods

Antimicrobial-resistant bacteria may be present in food even though antimicrobial residues are not detectable. Official testing for antimicrobial residues in foods of animal origin, including meat, dairy, honey and fish, is conducted under the National Residue Monitoring Programme. Results published in the 2012 report suggest that farmers adhere to the specified withdrawal periods for antimicrobial agents (DAFM, 2012). Tests were conducted in meat from all farm animal species during 2012. Of 5,821 bovine samples tested, 12 contained antimicrobial agents above the permitted threshold. Of 870 samples tested from sheep and goats, one exceeded the threshold (Residues Report, 2012).

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CHAPTER 6. THE INTERNATIONAL RESPONSE TO ANTIMICROBIAL RESISTANCE IN THE FOOD CHAIN

6.1   Introduction

Policies and actions related to control of antimicrobial use and AMR in the food chain have been developed in many individual countries and through inter-country cooperation at many levels, both European and global. This chapter presents an overview of the international response and a brief summary of the Danish experience as an example that may be informative for the development of policies and actions for Ireland.

6.2   Global Response

The global 'One Health' approach, which views health as an integrated whole, encompassing people, animals, agriculture and the wider environment across all countries, is a central element in approaches to dealing with AMR (Rushton, 2014; WHO, 2014; WHO, 2015).

The global focus on AMR has elicited a strong collaboration between the World Health Organization (WHO), the Food and Agricultural Organization of the United Nations (FAO), and the World Organization for Animal Health (OIE). The tripartite mechanism between the WHO, FAO and OIE is to promote the 'One Health' concept. Improved inter-sectoral collaboration is seen as fundamental to this. All organisations recognise the need for sharing responsibilities and coordination on global activities in relation to addressing the risks of AMR. Tripartite meetings have focused on recommendations, and ongoing development of an action plan to focus on a joint strategy on the containment of AMR. Prudent and responsible use in all sectors, surveillance data, and AMR risk assessment are amongst the steps for action proposed as well as the development and adoption of international standards and protocols.

In 2011, the Codex Alimentarius Commission (CAC) published guidelines for risk analysis to assess the risk to human health from foodborne antimicrobial-resistant microorganisms related to non-human use of antimicrobial agents and included appropriate risk management actions (Codex Alimentarius, 2011). The OIE Terrestrial Animal Health Code outlines standards for the improvement of animal health and welfare, as well as public health and welfare, with the 2013 edition containing chapters in relation to AMR considering risk assessment, harmonisation of AMR surveillance, monitoring of antimicrobial usage, and responsible and prudent use of antimicrobials (OIE/WHO, 2014). The OIE recommends that permanent risk assessment is carried out in parallel with the usage of antimicrobials, so as to ensure the health and welfare of animals in the context of a growing demand for animal protein, and global food security.

6.3   European Response

A key initiative of the EU to limit antimicrobial use in production of food animals was the ban on the use of antimicrobial agents as growth promoters in 2006. This measure was an important statement of principle but there is little evidence to demonstrate that it has resulted in a consistent EU-wide reduction in antimicrobial use in animal food production and some suggestion that an increase in use, categorised as therapeutic, neutralised much of the intended effect of the ban (Cogliani *et al.*, 2011).

In November 2011, the European Commission launched its five year action plan against the rising threat of AMR (European Commission, 2011). This plan details 12 actions to be addressed by both the human and veterinary sectors in each Member State, individually, and working together. In summary, the 12 actions focus on appropriate use and infection prevention in both human and veterinary sectors, the need for new antimicrobial agents and continued surveillance both of consumption and resistance development. The plan points to the need for international co-operation, research and innovation, as well as communication across all sectors. A report on the action plan was published in February 2015 (European Commission, 2015) detailing progress on each of the actions points.

The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established under agreement at the EU-US Summit in 2009. The objective of TATFAR is to increase mutual understanding of EU and US initiatives in relation to AMR issues. A set of 17 recommendations was agreed in 2011 (TATFAR, 2011) and a progress report was published in 2014 (TATFAR, 2014). This report identified the need for a new recommendation. It was recognised that the extent and mechanisms of transmission of AMR from animals to man remain poorly understood. A new recommendation was therefore agreed specifically to identify and address the knowledge gaps in this area.

6.4 Country Level Responses

Denmark has been at the forefront of initiatives on antimicrobial resistance in Europe in recent years therefore, the response in Denmark is considered in some detail in this section. Many other countries in Europe and elsewhere have also implemented relevant actions. A number of countries including Sweden and Finland had also acted to limit antimicrobial use many years before the current international consensus on the need for action on AMR was reached. In the interest of brevity, these are not described here but the bibliography includes relevant documents describing the actions in a number of these countries.

6.4.1 Denmark

Denmark has taken a number of initiatives to address the challenge of AMR over the last 20 years. Actions undertaken by the Danish authorities have been seen as a model by many in Europe.

In the early 1990s, Denmark documented a rapid increase in the use of antimicrobial agents and an increase in antimicrobial-resistant bacteria causing disease in animals. In 1995, Denmark established the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) (Nielsen *et al.*, 2007). This is a system for monitoring the development of AMR. DANMAP was established to follow the impact of withdrawing antimicrobial growth promoters. Comparable monitoring of AMR in humans began three years later. The aim was to inform future policy by measuring the effect of interventions.

With regard to monitoring consumption of veterinary antimicrobials, the veterinary medicines database VETSTAT was established in 2000 and is linked to the Danish herd database. VETSTAT is a national monitoring system of all veterinary drug use in Denmark (DANMAP, 2011; DANMAP 2012). Veterinarians, pharmacists and farmers send information within 30 days of use, which includes the prescribing veterinarian, herd, name of product; quantity prescribed and administered animal species, age group and diagnostic group. It is then possible to estimate Danish antimicrobial use for food-producing animals using this information. Caution however, should be used when interpreting trends in antimicrobial consumption over time, as there is potential for errors (such as incorrect data) or changes in animal populations.

The establishment of the DANMAP and VETSTAT systems has provided information to support veterinary risk analysis through centralised systems for monitoring AMR in food, animals and humans and for monitoring antimicrobial prescribing and use (Nielsen *et al.*, 2007).

The sale of veterinary medicines by a small number of veterinarians to livestock farmers was considered one factor contributing to the increased use of antimicrobials. Therefore, the Government took the legislative step to decouple prescribing and dispensing medicines by veterinarians in 1995 (Directive (DK) 60/1995 1995). Veterinarians are still permitted to sell medicines but the profit that they can make cannot be more than 5%, whereas prior to that time it had been 25%. Almost all medicines used in the livestock sector in Denmark are now sold directly to the farmer by a pharmacy (DANMAP, 2012). The income of veterinarians did decline on foot of the decoupling, but other measures taken established the focus on preventative health strategies with veterinarians acting in a specialist advisory role. As well as decoupling, the Government introduced a ban on the routine preventive use of antimicrobial agents in 2000. These changes were associated with reduction in antimicrobial use but the importance of decoupling in contributing to this reduction has been questioned (Beemer *et al.*, 2012).

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A study for the Ministry of Agriculture, Nature and Food Quality in 2010 concluded that decoupling of prescribing and supply of antimicrobial agents in Denmark in 1995 was associated with a reduction in usage of antimicrobial agents but that this measure was taken in conjunction with other measures, in particular the ban on use of antimicrobials as growth promoters in 1995.

In 1996, the Danish Food and Veterinary Administration developed evidence-based prudent use guidelines for pig specialist veterinarians. The Danish Treatment guidelines, which are revised annually, now cover all animal production sectors and are circulated to veterinarians. The Danish Treatment Guidelines established threshold values for acceptable herd usage of antimicrobial agents, which meant that there was a benchmarking system in place with a requirement for high users to take measures to reduce usage levels (Aarestrup et al., 2010).

Use of antimicrobial agents as growth promoters was phased out between 1997 and 1998 (DANMAP, 1998) so that by 1998 the livestock sector, with the exception of pig farming, had voluntarily stopped using all antimicrobial growth promoters. This was achieved without any long-term negative effect on animal health and welfare. The pig farming sector continued use of antimicrobial growth promoters until January 2000. Immediately following the ban, many pig herds had an increased incidence of disease leading to increased use of therapeutic antimicrobials, in particular amongst younger pigs. Implementation of changes in production practices such as later weaning and improved diet, were able to address this challenge over time (Bager, 2000; DANMAP, 2012). Actions taken in Denmark achieved a major reduction in the volume of antimicrobial use (of the order of 50%) and preceded by several years the EU-wide ban on use of antimicrobial growth promoters introduced in 2006 (Regulation (EC) No 1831/2003).

Restrictions were also placed on the use of specific antimicrobial agents considered important for use in the human population. Legislative controls were put in place in 2002 to restrict use of fluoroquinolones in food-producing animals to situations in which laboratory testing indicated that this class of antimicrobial agent was the only option for disease treatment (Nielsen et al., 2007).

As a result of detailed monitoring of antimicrobial consumption, the pig sector became a focus for action. In 2009, a target was set for a 10% reduction of antimicrobial use in pigs over five years. The pig industry voluntarily introduced a ban on the use of third and fourth generation cephalosporins in 2010 (DANMAP, 2011). Also in 2010 a 'Yellow card' initiative was developed by the Danish Veterinary and Food Administration, targeting the highest users of antimicrobials in pig production. Pig farms, where use exceeded the regulatory limit, were subject to increased monitoring, to various fees and to requirements to reduce antimicrobial use. The Yellow Card initiative has been very successful in reducing use (Nielsen et al., 2007). The limits for consumption are issued annually and have been adjusted several times. The target of a 10% reduction by 2013 was exceeded, with the use (in kg active compound) in Danish pig production in 2013 being 13% lower than in 2009 (DANMAP, 2013). A Red Card system was recently instigated whereby, if usage is excessive, the herd density is required to be reduced in order to reduce overall usage.

The Government made it compulsory in 2011 for each farm to have an individual herd health plan overseen by a nominated veterinarian who visited at a minimum of once a month. The herd health plan is intended to reduce the requirement for antimicrobial agents by prevention and control of infection through other methods. In 2014, a new risk management strategy was introduced which imposed differentiated taxes on medicines, with 0.8% on simple penicillins, 5.5% on most other antimicrobial agents, 10.8% on critically important antimicrobial agents but no tax on vaccines (Nielsen, 2014).

In summary, the Danish approach has been one of incremental change over 20 years, beginning with the establishment of systems for surveillance of antimicrobial resistance and antimicrobial use and a combination of a range of voluntary and legislative initiatives. The surveillance systems in place have enabled industry and regulators to determine if policy initiatives achieved the intended effects. There has been a focus on improving animal health in tandem with reducing antimicrobial use. The focus of measures is now moving towards control of critically important antimicrobials rather than the total use of antimicrobial agents with the use of scientific risk assessments for policy-making and increased research in animal health management.

There are many strategies in place at global, European and national levels intended to stem the spread of AMR and to preserve the efficacy of antimicrobial agents. All plans have similar objectives and recommendations whether they relate to human health, animal health and welfare or the environment, and all recognise that the global and 'One Health' perspectives are central. Although continuing to meet EU requirements with regard to surveillance of AMR and antimicrobial use, Ireland can learn from the experience of Denmark and other countries which have long been proactive in addressing this issue.

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CONCLUSIONS

It is well recognised that the use of antimicrobials can be important for both human and animal health. However, the use and misuse of antimicrobials in humans and animals, inadequate measures to control the spread of infection, combined with the innate adaptability of microorganisms, have resulted in a situation in which antimicrobials are less effective than they were. Without effective action, this situation is expected to worsen.

The scope of this document is limited to AMR in the food chain. In relation to antimicrobial use, the document has therefore, focused primarily on antimicrobial use in food production. The relative contribution of antimicrobial use in humans and animals to the development of resistance is unclear. In addition, although patterns of antimicrobial use in both human and animal health systems are different in different regions of the world, the relative contribution of practices in different regions to the scale of the problem is unclear. There is no doubt however, that the challenge of AMR requires an urgent global cross-sectoral response. The 'One Health' concept, which takes an integrated approach to the health of people, animals and the wider environment, provides a framework for such a response.

In the food chain, it is recognised that there are a number of challenges to reducing antimicrobial use. There are increasing demands for food production and increasing pressure on farmers to produce food at low cost. These factors can promote dependence on antimicrobial agents. However, it is recognised that a focus on improving animal health and welfare has the potential to reduce this over-reliance on antimicrobial agents, improve productivity and lower input costs.

In relation to antimicrobial use in Ireland, it is known from the available data on sales that use in food-producing animals is of the order of 100 tonnes per annum. This is a crude measurement; it does not capture differences in use among animal species. At present, data on use by animal species, stage of production and clinical reason for use are not available. Efforts are underway in the EU to address existing data gaps.

It appears that processes such as the application of withdrawal periods for veterinary medicines and the associated regulatory control mechanisms to avoid exposure of people to residual antimicrobial agents in food products are generally successful in Ireland. It is very uncommon to detect antimicrobial substances above threshold levels in domestically produced meat or milk. However, antimicrobial-resistant bacteria may still be present in food even though residues are not detectable.

In relation to antimicrobial-resistant bacteria originating from food animals, resistance to one or more antimicrobial agents is common in *Salmonella*, *Campylobacter* and the indicators, *E. coli* and *Enterococci*, from animals and food. The quality of data available from EU Member States is highly variable but the situation in Ireland appears broadly comparable with many other EU Member States.

Against this background, and with these limitations, the following conclusions were made on the basis of best available data/information:

1. Antimicrobial-resistant bacteria and free DNA fragments encoding AMR genes are transmitted in the food chain

2. The extent to which the food chain contributes to the overall issue of antimicrobial-resistant bacteria as a public health problem is not well defined

3. Acquired AMR occurs in response to antimicrobial use; therefore, measures to reduce antimicrobial use are central to responding to this challenge

4. Although the use of antimicrobials for growth promotion is no longer permitted within the EU, there is extensive use of antimicrobials in animal husbandry (primary production/pre-harvest level) for prevention and treatment of disease

5. In the EU and elsewhere, there is progress towards further restriction of use of antimicrobial agents, e.g. certain cephalosporins and fluoroquinolones, in food-producing animals. A number of countries have developed national strategies for control of AMR in the food chain. Some of the control measures employed elsewhere may be suitable for use in Ireland and warrant consideration at a national level

6. The National Interdepartmental Antimicrobial Resistance Consultative Committee, established by the Department of Health and the Department of Agriculture, Food and the Marine in 2014, is a key structure in the management of the problem of AMR in Ireland

7. Currently, the data in most EU countries on usage of antimicrobials in food-producing animals are based on recorded sales rather than actual usage data and are not animal species specific

8. Although the data on antimicrobial sales do not allow for a precise picture of animal sector specific use, it appears that in Ireland as elsewhere, a high proportion (approximately 50%) of sales by tonnage are intended for use in pigs. There is likely to be considerable scope for more prudent use in some sectors

9. Enhanced education, training and support for veterinarians and farmers on prudent use of antimicrobial agents are needed

10. The level of veterinary supervision required in Ireland in relation to intramammary use of antimicrobials and use of antimicrobials in feed premixes is less than that which applies to antimicrobial use in other prescribing scenarios

11. Although there is an existing legal requirement that those who supply veterinary medicines, including antimicrobial agents, accept return of unused medicines for safe disposal, it is not clear that this is always adhered to or enforced

12. At a national level, integrated surveillance and analysis of antimicrobial usage data from the food chain and human sources are inadequate

13. In the case of surveillance of antimicrobial-resistant bacteria, the harmonised system in place in the EU is focused on domestically produced food of animal origin, sampled at pre-harvest level. Expansion of the system to include surveillance of antimicrobial-resistant bacteria in raw meat at post-harvest level is being introduced in 2015. There is no corresponding system for food of non-animal origin

14. At present, there is no specific monitoring of foods imported into the EU for antimicrobial-resistant bacteria and no good evidence to allow comparison between imported and domestic food in this regard

15. The relative importance of transfer of antimicrobial-resistant bacteria to food during primary production, compared with contamination of foods with antimicrobial-resistant bacteria during washing, processing and preparation is unknown

16. Antimicrobial-resistant bacteria in animal manures and by-products and municipal organic materials may be deposited in the environment, including water sources. This is likely to be a factor contributing to the presence of antimicrobial-resistant bacteria in foods of non-animal origin. However, its relative importance is poorly defined

17. There is insufficient evidence to suggest that contamination of food from food handlers colonised or infected with antimicrobial-resistant bacteria contributes significantly to the spread of AMR

18. Measures aimed at reducing or eliminating pathogens and indicator organisms from food, i.e. GAP, GHP and HACCP-based procedures, should substantially reduce the risk of transmission of viable antimicrobial-resistant bacteria through the food chain

19. Existing evidence does not establish any of the following as likely to be important in the transmission of antimicrobial-resistant bacteria through the food chain: (a) bacterial cultures used in food production; (b) biocides used along the food chain; (c) free DNA fragments encoding AMR genes; or (d) AMR genes in genetically modified plants

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RECOMMENDATIONS

This report outlines the overall challenge of AMR, the evidence for transmission of AMR through the food chain and the extent of gaps in surveillance data. These recommendations represent an attempt to outline a balanced response and should be reviewed as more information becomes available. In line with the scope of this document, the recommendations are limited to antimicrobial use and AMR in the food chain. As there is no single measure to address AMR, stakeholders at each stage in the food chain need to take responsibility. Continuing emphasis on good agricultural practice, good hygiene practice and HACCP-based procedures is fundamental as these are key safeguards against transfer of bacteria including antimicrobial-resistant bacteria through the food chain.

The recommendations are linked to specific conclusions:

1. Wherever possible, the requirement for antimicrobial agents in food production should be reduced by improved animal husbandry and disease prevention measures [Conclusions - 3 and 4; Key stakeholders - farmers, veterinarians, and DAFM]

2. Wherever possible, intensive production systems should be designed to ensure that when antimicrobial use is necessary, the extent of use is minimised by ensuring that it is targeted to specific animals, as distinct from herd-/flock-wide administration [Conclusions - 3 and 4; Key stakeholders- farmers, veterinarians, and DAFM]

3. Enhanced systems to support prudent use of antimicrobial agents in food production, based on international best practice, should be further promoted, including:
    a. Provision of more education and training to relevant stakeholders, e.g. veterinarians and farmers, to improve understanding of the problem
    b. Production of veterinary antimicrobial prescribing guidelines for veterinary practitioners in Ireland, in consultation with key stakeholders. These guidelines should be made readily available
    c. Changing prescribing controls to ensure that the level of veterinary supervision required in relation to use of antimicrobial agents in premixes and intramammary formulations is equivalent to the level that applies in most other prescribing scenarios
    d. Establishing national and sector specific goals for more prudent use of antimicrobials in consultation with stakeholders
    e. The introduction of incentives to promote prudent use, as well as sanctions/disincentives for imprudent use, should be explored. This requires surveillance of use at veterinary practice/farm level. In the first instance, it may be appropriate to focus on large scale intensive animal production. Quality assurance and other relevant schemes may be a useful process to incentivise prudent use
    f. Provision of improved access to quality assured diagnostics to support more timely and targeted use of antimicrobial therapy
    g. Safe disposal of unused or unwanted antimicrobial agents should be further encouraged and facilitated [Conclusions - 3, 4, 5, 7, 8, 9, 10 and 11; Key stakeholders - DAFM, veterinarians, farmers, School of Veterinary Medicine, Teagasc, Bord Bia]

4. Surveillance of antimicrobial use in animals should be: (a) based on actual use rather than on sales data; (b) distinguished on animal species and stage of production/lifecycle. Timely and complete surveillance of use could be helped with the provision of electronic prescribing of antimicrobial agents. [Conclusion - 12; Key stakeholders - DAFM, veterinarians, farmers, School of Veterinary Medicine, HPRA]

5. A national integrated 'One Health' approach to collation and analysis of antimicrobial usage data from food chain and human sources should be introduced. In this context, a joint annual report could be used to achieve this [Conclusion - 12; Key stakeholders - DAFM, veterinarians, farmers, School of Veterinary Medicine, HPRA, Department of Health, HSE, HPSC]

6. Enhanced surveillance systems are required in Ireland to clarify occurrence and sources of antimicrobial-resistant bacteria in: (a) the food chain at pre-harvest and post-harvest stages, (b) in food of animal and non-animal origin and (c) in domestically produced and imported food. A national integrated approach to collation and analysis of data on the occurrence of antimicrobial-resistant bacteria in the food chain with data from human sources should be developed. A joint annual report modelled on the EU Summary Report on Antimicrobial Resistance in Zoonotic and Indicator Bacteria from Humans, Animals and Food, could be used to achieve this [Conclusions - 2, 12, 13, 14; Key stakeholders - DAFM, veterinarians, farmers, School of Veterinary Medicine, CVRL, FSAI, HPRA, Department of Health, HSE, HPSC]

7. Key research questions which should be prioritised at national and European level include:
    a. The relative importance of the food chain as a whole in contributing to the overall issue of AMR as a public health problem [Conclusions – 15, 16, 17]
    b. The extent to which systems for the disposal/recycling of animal manures and by-products and municipal organic materials, whether treated or untreated, contribute to the dissemination of antimicrobial-resistant bacteria in the food chain [Conclusions – 15 and 16]
    c. The impact of different routes of administration of antimicrobials (including intramammary) on AMR in the food chain [Conclusion – 9]
    d. Defining key drivers of veterinary prescribing behaviour and effective ways to achieve behavioural change [Conclusion – 8] [Key stakeholders – DAFM, safefood, Health Research Board, Environmental Protection Agency, Science Foundation Ireland, Teagasc, research institutes]

Report of the Scientific
Committee of the Food Safety
Authority of Ireland

Potential for Transmission of
Antimicrobial Resistance in the Food Chain

GLOSSARY

Antimicrobial Resistance
When microbes are less treatable with one or more medication used to treat or prevent infection

Antimicrobials
Refers to an agent or mechanism that kills or inhibits the growth or reproduction of microbes

Antibiotic
A drug used to treat bacterial infections, e.g. penicillin

'One Health'
The 'One Health' concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals and the environment

National Reference Laboratory
This is a laboratory that is responsible for coordinating the diagnostic standards and methods within their field of responsibility

Multi-annual Control Plan
Regulation (EC) No 882/2004 requires each Member State to prepare a single integrated multi-annual national control plan (MANCP). This plan must contain general information on the structure and organisation of the systems of feed and food control, and of animal health and animal welfare control in the EU Member States

Hazard
A hazard is a potential source of harm or adverse health effect on a person or persons

Risk
A risk is the likelihood that a person may be harmed or suffers adverse health effects if exposed to a hazard

Commensal
Living in a relationship in which one organism derives food or other benefits from another organism without hurting or helping it

Disc Diffusion
A method where a culturing surface inoculated with microbe is exposed to small disks containing known amounts of a chemical agent resulting in a zone of inhibition (usually in mm) of growth of the microbe corresponding to the susceptibility of the strain to the agent