Principles for risk assessment for antimicrobial resistance occurring in the food pathway

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I hereby declare that the work submitted is mine and that where I have made use of another's work, I have attributed the source(s) according to the Regulations set in the Student's Handbook.

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Dedicated to my family with special thanks

To Amalia, Annita, Konstantis, and Vangelis

Abstract

This dissertation was written as part of the MSc in in Bioeconomy Law, Regulation and Management at the International Hellenic University.

Antimicrobial resistant bacteria are of public health concern, since they can be biological hazards linked to increased human mortality and morbidity. Use of antimicrobials for control and treatment of infectious diseases in livestock and crops goes on due to considerations with respect to animal health and welfare, and also plant health. As a result, the dissemination of antimicrobial resistance by transfer of bacteria or genes from animals or plants to humans through the food chain is a public health issue of major concern. The dissemination of antimicrobial resistant bacteria and resistance genes to humans via food can follow several different routes and mechanisms, by foodborne spread of: i) resistant zoonotic bacteria, ii) resistant non-zoonotic human pathogenic bacteria and iii) commensal bacteria that exhibit resistance due to transferable antimicrobial resistance genes. Risk assessment is a scientific tool that its purpose is to provide risk managers with a rational and objective picture of what is known, or believed, at a particular time. Risk assessment can be quantitative or qualitative with the process being essentially similar since both procedures involve identification of the risk pathway, collection of data and risk evaluation. Qualitative risk assessment provides a rough estimate of risk, using definitions like high, medium and low risk and uses all relevant data (including numerical data) in order to reach a inference. The aim of this dissertation is to identify the principles of risk assessment for antimicrobial resistance occurring in the food pathway; to identify i) the qualitative risks, ii) the direct and indirect hazards, iii) the pathways of exposure; to summarize data in order to evaluate size of the hazard to which humans are exposed, and to assess the further consequences of resistance.

Keywords: risk assessment, antimicrobial resistance, resistance genes, hazard, foodborne.

Panagiota Gousia

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Preface

The dissertation "Principles for risk assessment for antimicrobial resistance occurring in the food pathway" was written to fulfil the graduation requirements of the Master of Science (MSc) in Bioeconomy Law, Regulation and Management. I was engaged in researching and writing this dissertation from June to November 2018.

I attended the Master of Science (MSc) in Bioeconomy Law, Regulation and Management during 2017 to 2018, with a scholarship I received from the Ministry of Rural Development and Food and the International Hellenic University. My dissertation was formulated together with my supervisor, Professor Fragkiskos Kolisis. In the difficult task of conducting and writing this research, both Professor Fragkiskos Kolisis and my master course tutor, Dr. Savvas Genitsaris, have aided me considerably.

I would like to thank my supervisor Professor Fragkiskos Kolisis for his excellent guidance and support during this process. Dr. Savvas Genitsaris for his support during the entire course of Bioeconomy. All my fellow students, without whose cooperation I would not have been able to conduct this dissertation. It was always helpful batting ideas around with them.

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Contents

1. Introduction and Definitions

Antimicrobial resistance (AMR) is no longer just a potential threat; it is a serious health problem that is rapidly increasing across the world (Butaye et al, 2015). This is a major global public health concern and a food safety issue since pathogens can become resistant to antimicrobial agents and pose a greater human health risk. The threat to human health consists of potential treatment failure due to inappropriate antimicrobials, lack of treatment choices and increased harshness of disease (O Neil, 2016).

A resistant bacterium is the one that can stand higher concentrations of an antibiotic than other, phenotypically related bacteria of the original or "wild type" strain (EFSA, 2008). Such strains usually differ phenotypically from the wild type. Not only that they usually have acquired a resistance mechanism by gene transfer or by mutation (acquired resistance).

Acquired resistance. There are two mechanisms by which a bacterial isolate can acquire resistance: mutation or acquisition of exogenous genes by horizontal transfer from other bacterial strains. The genes that encode the enzymes responsible for the modification of the structure of an antimicrobial and therefore the tolerance of the bacterium to it, can be easily transferred. Such transferable genes are the ones encoding penicillinases and cephalosporinases (*bla* genes), acetyl transferases responsible for aminoglycoside modification (*aac* genes), genes that can lead to modification of the antibiotic target (*erm*-genes), methicillin resistance (*mecA* genes) and resistance to glycopeptides (*van* genes).

Cross resistance. Since antimicrobials are a quite diverse group of molecules, they are classified in classes that usually categorize substances with similar structure and mode of action. It is not uncommon that the antibiotics in each class share a common target in the bacterial cell and a similar mode of action. Therefore, resistance to a antimicrobial usually is accompanied by variable resistance to the other antimicrobials of its class.

Corresistance. The resistance genes are often organized in larger genetic elements that can be transposons, integrons or plasmids. Since they are gathered in

these structures, unrelated resistance genes are co-acquired resulting to resistance in phenotypically unrelated traits. Therefore, a single transfer of e.g. a plasmid can result to transfer of several resistance genes. The term corresistance is therefore used when two or more different resistance genes are physically related (EFSA, 2008).

Multiple resistance. Multiple resistance is the term used to declare that a bacterium is resistant to more than two different antimicrobial classes. Quite often it is also used to describe a strain resistant to more than two antimicrobials, but due to possible cross resistance this definition is less accurate. The references to the definition vary considerably, making the use of this term quite problematic.

Antimicrobial resistance genes. Genes in bacteria conferring resistance to antibiotics. They are usually located on mobile genetic elements, and because of that they have the ability of horizontal transmission from resistant to susceptible strains.

Empirical therapy. Therapy introduced on the basis of observation of clinical symptoms and patient's history, without verification of diagnosis by laboratory diagnostic methods.

Hazard. A physical, chemical or biological agent in food potential to cause an adverse health effect.

Risk. A function of the likelihood of a harmful effect and the importance of that effect, resulting to hazard in food.

Risk Analysis. A process consisting of risk assessment, risk management and risk communication.

Antimicrobial resistance has been linked to use of antibiotics in almost any environment. Antibiotics are used for human and non-human purposes. A not much sought risk factor is the use of antibiotics in food animals. In addition, their use in agriculture has been also neglected since they can contribute to selection and spread of antimicrobial resistant microorganisms. Both food producing animals and farming can introduce resistant bacteria or genes in the food chain and unavoidably to humans (Anonymous, 2011).

Transmission of resistant bacterial cells to humans and especially to human gastrointestinal tract is of importance due to either direct infections or the likelihood of horizontal gene exchange with other, potentially pathogenic members of the gut

microbiota promoted by the high number of cells found in the gut (Aarestrup et al., 2008; Collignon et al., 2016).

*Risk assessment. T*he scientific analytical process to evaluate the chance of adverse effects from exposure to a hazard such as physical, chemical or biological agent) or hazardous event (Claycamp, 2015).

2. Antimicrobial resistance in food

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Antimicrobial resistance in commensal, opportunistic bacteria or obligate pathogens is an increasing public health concern due to the likelihood of antimicrobial resistance gene transfer from commensal bacteria to pathogens or between pathogenic bacteria (Friedman, 2015;). Food stuff occupies a serious role in the transmission of both commensals and foodborne pathogens. Transmission of commensal microorganisms among food and humans happens during handling of raw products; during cross contamination and recontamination between different food materials at different stages of the food supply chain (Macdonald et al., 2015). A food supply chain refers to the processes which describe how food from a farm ends up on our tables (production, processing, distribution, household levels e.g. consumption and disposal). Transmission of antimicrobial resistant bacteria to humans and especially to the human gut is a matter of interest due to direct infections but also due to the chance of horizontal transfer of genes to other pathogenic members of the gut microbiome (Haug et al., 2011; Collignon et al., 2016).

Various European countries carry out surveillance programs for antimicrobial resistance like Anresis in Switzerland, Swedres Svarm in Sweden, DANMAP in Denmark (Danmap, 2014; Swedres-Svarm, 2015). Data from European countries are further collected, organized and evaluated under the umbrella of the European Centre for Disease Control (ECDC) and European Food Safety Authority (EFSA) to prepare comprehensive annual reports on antimicrobial resistance prevalence in animal isolates, raw meat isolates and human ones (EFSA and ECDC, 2016). The One Health approach has become an inseparable part of antimicrobial resistance surveillance so as to match up with surveillance reports, approaches and interventions in human and veterinary medicine (Zinsstag et al., 2011). A more further approach is done by the Canadian Integrated Program for Antimicrobial Resistance (CIPARS) which proposes including the environment, the wildlife, the feed, the companion animals and also water and food into their antimicrobial resistance surveillance program (Deckert et al., 2015). However there are no specific microbial monitoring programs at the retail level to determine exposure of consumer to antimicrobial resistant foodborne bacteria.

Most food antimicrobial resistance monitoring programs are limited to studies of resistance to samples of raw meat (Federal Office of Public Health Foph Division Communicable Diseases, 2015; EFSA and ECDC, 2016). The study of foodborne microorganisms in the retail sector would greatly help to identify possible transmission routes between animal and human microorganisms via food and would further improve the strategies for limiting antibiotic resistance in line with the objective of the One Health concept (Jans et al, 2018).
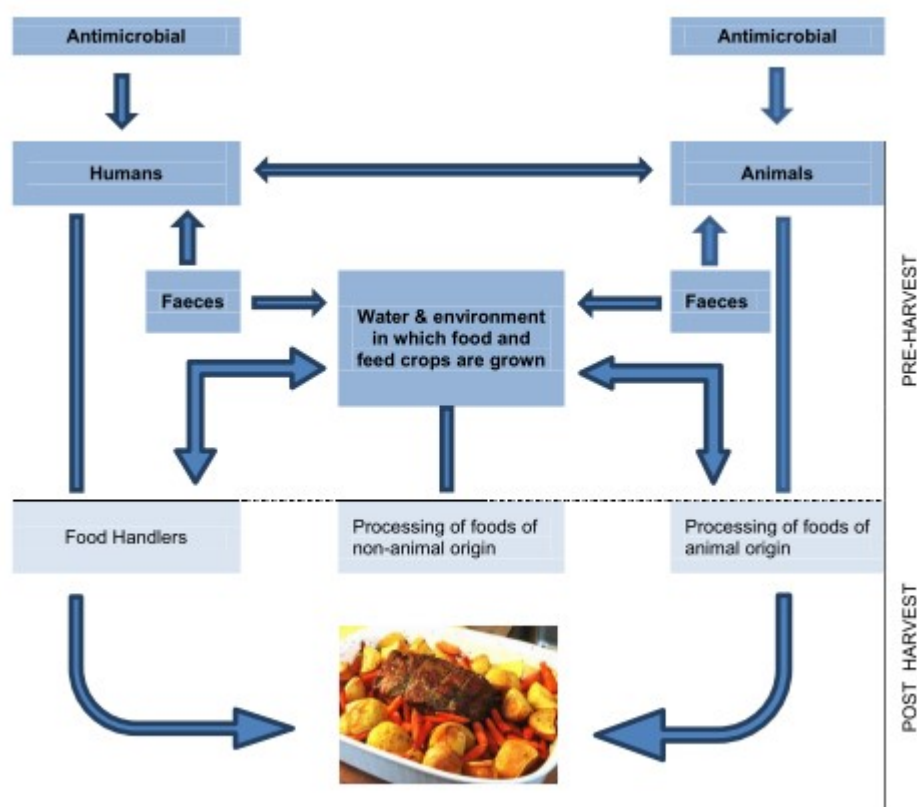
Picture 1. Potential routes of transmission of antimicrobial-resistant bacteria via the food chain (EFSA, 2008)

Proper use of antibiotics in most sectors, such as agriculture, stockbreeding, medicine, would greatly maximize human health benefits by reducing the pace and delaying the spread of antibiotic resistant strains. Foods can be contaminated with antibiotic-resistant strains during primary production as well as in later stages of the supply chain. Contamination of foods of animal origin with resistant bacteria is more likely in food from animals that have received antibiotics. However, resistant strains can be transmitted to other non-antimicrobial animals. In addition, it has to be known

that the resistant strains have the ability to evolve in an external or internal environment for long periods of time. Correspondingly, foods of plant origin are likely to be contaminated by organic matter such as manure, water, urban sludge containing antimicrobial resistant bacteria (Irish Food Authority, 2015).

Good Agricultural Practice (GAP), Good Hygiene (GHP) and Risk Analysis and Critical Control Point (HACCP) procedures are measures aimed at reducing or eliminating the antimicrobial resistance of food-producing strains and, in particular, eliminating of pathogens and of marker micro-organisms in food. Good practice can significantly reduce the risk of AMPB transmission through food. Thus, good hygiene during slaughter and skin carcassing can minimize the transport of bacteria, and thus also of resistant bacteria. In addition, foods that are adequately cooked, pasteurized or are subject to some form of microbicidal treatment, such as high pressure processing, are extremely difficult to transport live AMRBs from their early stages of production (e.g. primary production).

In addition to resistant bacteria originating from primary production, there are other possibilities to contaminate food. Thus, cooked or processed foods during storage, preparation and disposal are likely to become infected with AMRB. In addition, drinking water can be a carrier of resistant bacteria, especially when infected with fecal (human or animal) strains. Water from drilling on crops or the use of this water in food processing as a food ingredient favors the transport of AMRB to food. AMR risk management requires monitoring of the use of antibiotics in the food chain as well as the occurrence of AMRBs isolated from food and animals. Directive 2003/99/EC and Commission Implementing Decision 2013/652/EU require monitoring of antimicrobial resistance in specific zoonotic pathogens and indicator bacteria isolated from food of animal origin and animals. The European Food Safety Authority (EFSA) publishes these results every year in EU annual summary reports on antimicrobial resistance in zoonotic, animal indicator bacteria and food indicator bacteria. The requirements related to AMR monitoring are harmonized for countries with regard to methodology, tested microorganisms, sample populations, and interpretative criteria (Irish Food Authority, 2015).

2.1.   Transmission of antimicrobial resistance

The use of antimicrobial agents in various hosts is the most important factor influencing the emergence and spread of antimicrobial resistance by spreading resistant bacteria and genes of resistance between hosts not only of the same but also of different species (SSC, 1999). Antimicrobials can be dispensed and applied in a variety of ways in the human medicine, veterinary medicine and horticultural practice. Antimicrobials are used for therapy and prophylaxis against infection. The level of supervision is variable since antibiotics are used in certain premises, including hospitals and the community (EFSA, 2008).

Table 1. The main animal reservoirs and transmission routes from food producing animals to humans of antimicrobial resistance hazards

	Food producing animal reservoirs	Transmission route
Livestock associated MRSA*	Pigs, veal calves, and broilers	Direct contact
Quinolone resistant *Campylobacter jejuni*	Poultry, pigs, veal calves, and dairy cows	Food of animal origin
ESBL+ *Escherichia coli*	Broilers, veal calves, pigs, and dairy cows	Food of animal origin and/or direct contact
ESBL+ *Salmonella* spp.	Poultry	Food of animal origin

* methicillin resistant *Staphylococcus aureus*

Different types of microorganisms can exchange antimicrobial resistance traits. The main pathways by which humans can get contaminated include person-to-person transmission, the environment, and contact with animals, including food producing and domestic animals.

Aarestrup (2006) has provided an extensive review of different pathways by which AMR bacteria can be transmitted to humans. AMR transmission usually involves contamination by AMR bacteria. Therefore good hygienic practices are extremely important in order to control and prevent foodborne AMR contamination.
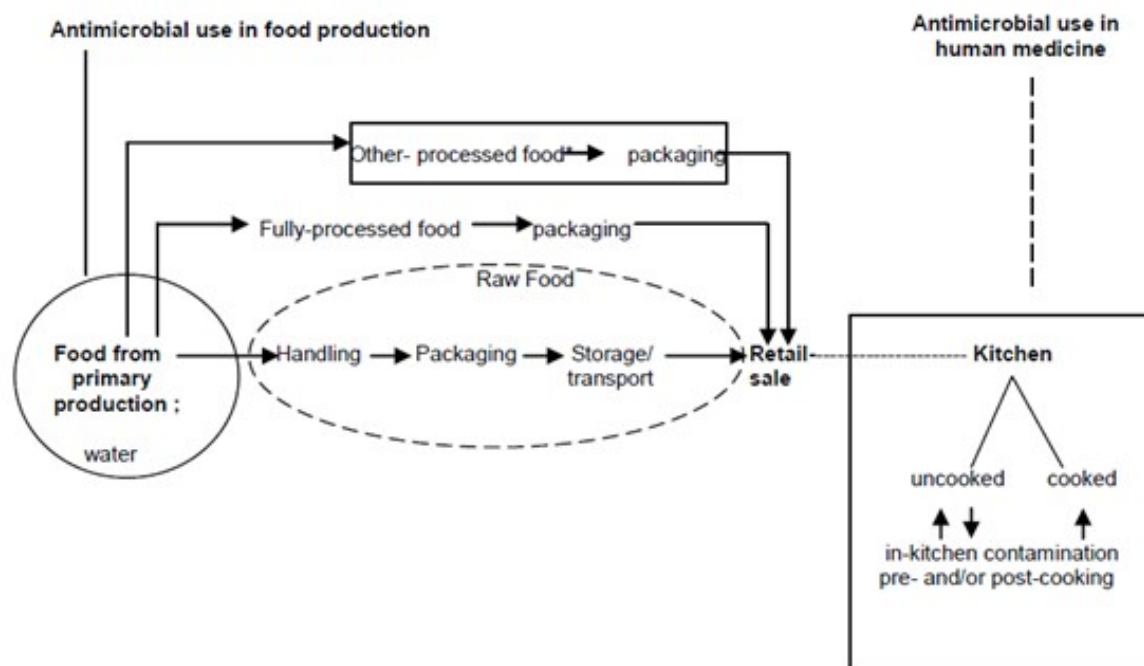
Picture 2. Possible transmission of antimicrobial resistance via food (EFSA, 2008)

2.2.   *Food of plant origin*

Resistant bacteria from various sources can contaminate foods of plant origin. The soil is loaded with microorganisms which may harbor antimicrobial resistance genes. Food contamination may happen after direct contact of edible portions of plants with soil and soil splash. Wastes from animals and human introduced as soil amendments or through animal presence provide another pathway for AMR organisms to **contaminate** food of plant origin. Water utilized for irrigation may also be **contaminated** with AMR bacteria. The adoption of good agricultural practices which limit total microbial contamination of foods of plant origin is a basic initial phase in diminishing the introduction of AMR organisms into food.

Unfortunately, there are few reagents for treating plants' bacterial infections. Among plant pathogens, antimicrobial resistance is reported for products used in treating bacterial diseases e.g. tetracycline, kasugamycin, streptomycin, and copper. In respect to antifungals, resistance to fungicides triazole is also relatively common, although there seems to have a large variation in the occurrence of resistance between different regions.

There are programs to minimize antimicrobial resistance risks. *Biological* control, with the introduction of organisms providing direct antagonism, competition and *biorational* products, e.g. plant extracts are alternatives that may prevent plant diseases. However, these products are generally far less effective (FAO/WHO, 2018).

2.2.1. Contamination of crops with bacteria resistant to antimicrobials

The microbiological contamination of fruits, vegetables, lettuce and in general of foods of plant origin that are consumed raw or undercooked is responsible for many foodborne outbreaks including disease caused by antimicrobial-resistant bacteria. Besides, produce at retail may also be contaminated with commensal bacteria that carry resistance to medically important antimicrobials (Verraes et al., 2013; Thanner et al., 2016). Fungi and bacteria cause worldwide significant plant disease and production losses, especially in low- and middle-income countries (LMICs). Climate change is possible to exacerbate the problem and the use of antimicrobial agents is expected to rise because older treatments become ineffective. There is growing concern that antimicrobials are losing their effectiveness in all sectors, not only in horticulture, but also in veterinary and human medicine. Extensive use and misuse of antimicrobials drives the development and transmission of antimicrobial resistance, but it is unclear the extent to which antimicrobial use is driving the development of antimicrobial resistance in spoilage organisms, soil organisms, plant pathogens and non-pathogenic contaminants and zoonotic agents present on foods of plant origin. Some of the same antimicrobial agents that are used in human and veterinary medicine, like streptomycin, tetracyclines, triazoles are also used to control plant diseases. Consequently, resistance developed in one sector can be transferred across sectors and species. Through processes of co-selection and cross-resistance, resistance developed to one antimicrobial may also render an organism resistant to several other antimicrobial drugs and chemicals. Bacteria, notably zoonotic organisms with resistance to one or multiple antimicrobials, are found on fruits, vegetables, and other edible plants, as well as in soils. The frequency with which resistant bacteria of plant-origin colonize the human gastrointestinal tract or serve as reservoirs of antimicrobial resistance genes in the gastrointestinal tract needs to be further investigated. There is persuading proof that horticultural antimicrobial use is driving the development of

antimicrobial resistant fungi that are transmitted increasingly from the environment to humans (FAO/WHO, 2018)

2.3.   Food of animal origin and antimicrobial resistance

2.3.1. <u>Antimicrobial use in food producing animals</u>

The use of veterinary medicinal products can give rise to risks for human health, food safety, the environment, animal health and welfare. In productive animals when there is a need for treatment, the use of antimicrobials is an important factor in the development of resistance to the microbial population. Treatment should be done correctly using the appropriate dosage and administration time. (Geenen et al, 2010)

2.3.2. <u>Critically important antibiotics in Veterinary medicine</u>

While WHO created the list of critically important antimicrobial agents, the OIE has built up a list in veterinary medicine, that of critically important antimicrobial agents in veterinary medicine. The aim of this list is described as "The overlap of critical lists for human and veterinary will give additional information, allowing an acceptable balance to be struck between animal health requirements and public health priorities"(FAO/OIE/WHO, 2004).

Since the majority of OIE Member States recognized the importance of using antibiotics while being considered necessary for certain infections, because of the absence of other alternative therapeutic options, it classified a category of antibiotics as veterinary critically important drugs. Veterinary Highly Important Antimicrobials were antimicrobials when solely one of the two criteria applies (that is either thought important by a majority of the member states of being critically or considered essential for the treatment of certain diseases without having equivalent alternatives). The rest antimicrobials were classified as veterinary important (OIE, 2007). Antimicrobial classes as categorized by the OIE are shown in the following site https://www.oie.int/doc/ged/D9840.PDF (Table 2).

Table 2. Categorization by the OIE of veterinary important antimicrobials for food-animals

Veterinary Critically Important	aminoglycosides
	cephalosporins
	macrolides
	penicillins
	phenicols
	quinolones
	sulfonamides
	tetracyclins
Veterinary Highly Important	rifamycins
	fosfomycinionophores
	lincosamides
	pleuromutilins
	polypeptides
Veterinary Important	bicyclomycin
	fusidic acid
	novobiocin
	orthosomycins
	quinoxalines
	streptogramins

(OIE, 2007)

Table 3. Classes and subclasses of antimicrobials classified as critically important for human medicine:

Beta-lactam	penicillin, cephalosporin (3rd and 4th generation) carbapenem, penem
Aminoglycoside	
Tetracycline	(tigecycline only)
Macrolide and ketolide	
Glycopeptide	
Quinolone	
Lipopeptide	
Oxazolidinone	
Streptogramin	
Ansamycin	

(OIE, 2007)

2.4.   Spread of resistance

Antimicrobial resistance spread between animals and humans may occur by transmission of resistant bacteria or by transfer of the antimicrobial resistance genes. Resistant bacteria transmitted from animals to humans may cause disease in humans, e.g. zoonotic resistant bacteria and pose a direct hazard. Transmission of resistant bacteria may occur through direct contact, environmental or food routes. Foodborne bacteria of animal origin, that do not cause human disease, but are likely to transfer resistance genes to human pathogens are indirect hazard, e.g. horizontal gene transfer.

2.4.1. Mechanisms of gene transfer

Resistance gene transfer may occur through vertical or horizontal transfer of genes. The gene transfer from bacteria to their offspring is known as vertical gene transfer. The exchange of genetic material from a bacterium acing as donor to a bacterium-acting as recipient, but which is not its offspring is known as horizontal transfer of genes. The main mechanisms for horizontal gene transfer are: i) conjugation, ii)

transduction and iii) transformation. In conjugation, the genetic material is moved among bacteria by a temporary linkage between a bacterium donor and recipient bacterium. In transduction the genetic material is moved by bacteriophages, and in transformation the genetic material is moved by uptake of free DNA. The most frequently reported mechanism of antimicrobial resistance gene transfer is conjugation and may take place between bacteria of different species or of different genera (EFSA, 2008b). During conjugation, plasmids or transposons can be transferred, as mobile genetic elements. Integrons which are gene capture systems found in plasmids, chromosomes and transposons and are of considerable importance in the dissemination of antimicrobial resistance genetically linked, by capturing, mobilization, and expression of resistance genes (Kovalevskaya, 2002). Published gene transfer rates during conjugation were found to vary widely (Hunter et al., 2008).

The dissemination of various resistance genes among different bacterial species is due to horizontal gene transfer (Barlow, 2009). Specifically, the gastrointestinal tract is a major hot spot for horizontal interspecies and intraspecies gene transfer.

2.4.2. <u>Transmission via food of animal origin</u>

Foodstuffs produced from food producing animal pose an important mean for the transmission of zoonosis, including resistant zoonotic bacteria, like *Salmonella* spp and *Campylobacter* spp. Besides, food is potential to conduce to resistance transfer in commensal bacteria, as resistance genes are mainly found on mobile genetic components. Besides, high numbers of bacteria existing in the gut promote the transfer of genes.

Transmission can happen during consumption or even handling of food contaminated with resistant bacteria. Both food handlers as well as the general population can be exposed. A possible reservoir may be food handlers themselves and cause foodborne diseases among the general population. The extend of consumers' exposure to antimicrobial resistant contaminated food, depends on various factors during food processing (Geenen et al, 2010).

Transmission during slaughter, food processing and food handling: Food can become contaminated with resistant bacteria from the faecal material of food-producing animals or from humans. The main point of dissemination of food animal

fecal material is during slaughter. The main point where food becomes contaminated with human faeces is during food handling. Therefore, food handling is a common way of introducing resistant bacteria into food for bacterial pathogens with a human reservoir (CAC, 2001).

Table 4. Food categories of animal origin and transmission pathways (Roberts, 1990)

Food categories of animal origin	Transmission pathways
Milk / dairy products	Milk is contaminated with bacteria of animal origin and human consumes soft cheeses made of raw milk or raw milk
Egg / egg products	Bacteria are transferred transovarial to egg content and human consumes raw or undercooked egg
Red meat	Carcass is contaminated with faecal content during slaughtering. Human consumes raw or undercooked meat or cross contamination may happen during food preparation.
Poultry meats	Carcass is contaminated with faecal content during the slaughter process. The consumption of inadequately cooked meat or cross contamination during preparation food, may happen.
Fish	Aquatic environment is contaminated with faecal bacteria and raw fish is consumed. In shell fish, concentration of faecal bacteria through filterfeeding, Consumers eat raw or inadequately heated shell fish.
Mixed / buffet meals	Usually one of the previous mentioned pathways and consumption of inadequately stored or inadequately heated meals happens

http://ilsi.eu/wp-content/uploads/sites/3/2016/06/MRA-Tools.pdf

3. Risk assessment

It is widely recognized that risk assessment is as a systemical way to organize and analyze information aiming in making regulatory decisions, establishing programs and prioritizing research and evolvement (USEPA, 2014).

3.1.   Introduction to Risk Assessment

In the field of microbiological food safety, significant developments in control measures applied to food have been made. Measures and approaches used in food safety were based on Good Manufacturing Practice, Good Hygienic Practice, as well as on the execution of a Hazard Analysis Critical Control Point (HACCP) system.

Risk analysis includes "risk management" and "risk communication" as associated concepts. Risk assessment occurs within a risk management context, to help decision-making on organizing a microbiological hazard and takes into account the character of the hazard and the probability of being exposed to that hazard. Microbiological risk assessment can vary from a single skilled judgment to a more investigative quantitative and qualitative risk assessment (CAC, 1999). The risk assessment process according to Codex document lists the following steps in: statement of purpose, hazard identification, hazard characterization, exposure assessment, risk characterization.

3.2.   Process of Foodborne antimicrobial resistance risk assessment

The risk assessor should consider, at the beginning, the profile of the risk, the documented information during commissioning the risk assessment and the risk assessment policy. A preliminary investigation is required to define and organize the work to be done within the framework of the foodborne antimicrobial resistance risk assessment. Foodborne antimicrobial resistance risk assessment comprises of hazard identification, exposure assessment, hazard characterization and risk characterization. The second and third phase (exposure assessment and hazard characterization) can be done alongside. The choice of a quantitative or qualitative approach is mainly based on the type of questions to be answered and also on the available data.

Risk assessment is a decision tool that provides risk managers with a logical and unbiaesd picture of what is known at a particular time. A risk assessment will not have all information given about a certain risk issue due to the fact that there are cases of limited access , like unwillingness of data owners to give information or because of lack of data (FAO, 2009). Sometimes it is insufficient for the managers to select a strategy, due to the fact that the information known at a particular time is insufficient. If the criteria for making a decision are well set, a risk assessment based on knowledge at that particular time, may provide guidance information to choose the correct decision more obviously (FAO, 2009).

3.3.   *Antimicrobial resistance risk assessments framework*

As already said, antimicrobial resistance risk assessment is a scientific tool to evaluate the health risks (qualitatively or quantitatively) after exposure to resistant microorganisms or resistance genes (Geenen et al, 2010). At the beginning of a risk assessment, an important step is making a risk management question. That question should determine the hazard but also the linked consequences to be investigated, and besides other information like the source, the population at risk, the country, the time period. The risk question may consist of two parts, the frequency and the consequences, for example:

1. What is the contribution of the use of cephalosporin in broilers in Greece in 2017-2018 to resistance of *E. coli* in respiratory infections?
2. What is the likelihood of adverse effects in human as a sequela of these infections?

Antimicrobial resistance risk assessment follows a similar four-step framework as used in Codex (2009). This framework is mainly established for foodborne transmission, but it could also be a guide for risk assessment related to transmission through the environment or through direct contact (Geenen et al, 2010).

3.3.1. Hazard identification

Hazard identification is the first step, which aims to identify the resistance hazard. But what could be a hazard? It could be a resistant bacterium but also a resistance gene (Geenen et al, 2010). Risk assessor reviews surveillance programs, literature and other information to identify certain strains or genotypes of foodborne bacteria that may be

risks by a certain food pathway, resistant to antibiotics microorganism or determinants or agents to which resistance is expressed. Besides, the biology of the resistant microorganisms or the determinants in various environmental conditions and the information on the susceptible strains would be helpful (CAC, 2011).

Direct and indirect hazards: Foodborne antimicrobial resistance is either a direct or an indirect hazard. The direct hazard is the presence on food of antibiotic resistant pathogens which may colonize or infect a human, after consuming of foodstuffs, or as a hazard arising through handling of contaminated food and the person acquires an infection. Indirect hazard happens when a bacterium resistant to antibiotics can transfer resistance genes to a pathogen directly, or through another commensal bacterium. In the case described above, the resistance gene is the hazard (EFSA, 2008; CAC, 2011).

3.3.2. Exposure assessment

Exposure assessment is the second step. Exposure assessment recognizes the routes of exposure and sums up the data for the certain routes so that it evaluates the frequency and the size of the hazard to of human exposure. It should take into consideration all reservoirs (humans, pets, food animals, environment etc.), all possible routes of the hazard to the population of importance, and, in the case of resistance genes, it should be considered the potential transfer of genes to human pathogenic bacteria. This poses antimicrobial resistance risk assessment very complicated; although the complexity can be decreased by concentrating in the main transmission pathways (Geenen et al, 2010).

Antimicrobial usage happens in various sectors in agriculture and at different stages of food supply. Following antimicrobial use, the selection of antimicrobial resistant microorganisms may occur, and after, they are able to disseminate among animal feed and food animals, or between food animals and sewage , that are going to be spread on crops etc (CAC, 2011).

3.3.3. Hazard characterization

The aim of the third step, the hazard characterization, is to define the probability of the disease as a consistence of the hazard exposure. Antimicrobial risk assessment should include the further sequels of resistance, e.g. severity of the disease and increased frequency of the disease (Geenen et al, 2010). According to Codex Alimentarius, in this step the characteristics of the hazard, the host and the food matrix are considered so as to define the probability of human disease. A hazard characterization related to foodborne antimicrobial resistance comprises also the features of the acquired resistance. It estimates the additional consequences that may happen when human is exposed to pathogenic bacteria resistant to antibiotics, such as severity and increased frequency of disease (CAC, 2011)

3.3.4. Risk characterization

The final step is risk characterization. The results of the previous steps have been integrated, in particular and an overall evaluation of risk is derived. Risk characterization answers questions containing uncertainties and other agents which may influence the risk management decision (Geenen et al, 2010). According to Codex Alimentarius (2011), risk characterization is the last step and consults the key findings from the previous steps (hazard identification, exposure assessment and hazard characterization) to evaluate the risk.

3.4.   Antimicrobial resistance risk assessment methodology

Antimicrobial resistance risk assessment of foodborne isolates can be either quantitative or qualitative, depending on the output expressed, either numerically or in qualitative terms. The output's quality is based on the data availability and quality. Most important data limitations in antimicrobial resistance risk assessment are microbiological methods used, small sample sizes large variability in sampling methods, low compatibility in resistance data and little data on indicator organisms, uncertain on reasoning, insufficient data on antibiotic use, lacking test sensitivity or specificity. The identification of data gaps is an important output of risk assessment which is very helpful in continuing research and collection of data. Limitations of data

can be exceeded using expert opinion, substitute data like data on related species resistance gene, on susceptible organism of the same species, predictive mathematical modelling (Snary et al., 2004).

In foodborne antimicrobial resistance risk assessment data, there are various sources of uncertainty. A helpful tool, by which the effect of uncertainty in the model input on the model output can be investigated, is done with sensitivity analysis. Some sources of uncertainty mentioned are: the large number of indirect routes, the quantification of resistance gene transfer within the animal gut or the human gut, and the probable enlarged time period between exposure and infection because of the resistance in commensals (Claycamp and Hooberman, 2004).

3.5.   *Overview available AMR-risk assessments in the literature*

An overview of the available foodborne antimicrobial resistance risk assessment is given in table 5. For the selected hazards, antimicrobial resistance risk assessments are only available for quinolone-resistant *Campylobacter* spp.

Table 5. Overview of available AMR risk assessments evaluating the human health risk/source attribution of antimicrobial use in food animals concerning *Campylobacter* resistance (Snary, 2004).

Resistance	Food animal	Funding	Qualitative/ Quantitative	Risk management question	Conclusion	Reference
Quinolone	Cattle	Industry	Quantitative	What is the potential public health risk from *Campylobacter jejuni* and fluoroquinolone resistant *C. jejuni* because of fresh beef and ground beef consumption?	After 10 years of fluoroquinolone use in beef cattle, 280 individuals and 45 hospitalized cases need additional therapy and/or longer hospitalization, and there is one associated death	(Anderson et al., 2001)
	Poultry	Government	Quantitative	What is the human health impact of fluoroquinolone resistant *Campylobacter* in broilers in 1998/1999 in the USA?	In the total population, 1 in 34,651/26,639 persons were affected; 1 in 23/17 cases seeking care and prescribed an antibiotic were affected	(Vose et al., 2001[a]; Bartholomew et al., 2005)
	Poultry and pigs	Government	Quantitative	What is the contribution of the food chain to quinolone resistance in microorganisms causing human infection relative to other pathways?	Attribution: exposure abroad (59.6%), chicken meat (8%), pets (3.6%), clinical treatment (1.5%). Pig meat, public water and crop consumption not significant	(VLA, 2004)
Macrolide	Poultry		Qualitative	What is the risk of transmission of macrolide-resistant *Campylobacter* from pigs to man?	Transmission through pig meat and environment (slurry/ waste) has no or a very low risk to man	(Burch, 2002)
	Poultry	Industry	Quantitative	How is food animal illness related to human foodborne disease? Example: macrolide resistance in *Campylobacter*.	The removal of macrolide feed additives in chickens could harm human health by increasing the level of contaminated chicken	(Singer et al., 2007)
	Poultry, pigs and cattle	Government	Quantitative	What is the potential human health risk due to foodborne *Campylobacter* spp. infections from on-farm use?	The human health risks due to macrolide induced resistance in *Campylobacter* are extremely low.	(Hurd et al., 2008)

4. Description of the microbiological hazards

4.1.   Direct hazards

Antibiotic resistant bacteria spread from animals to humans under ordinary conditions can cause human disease, known as zoonotic diseases or zoonoses, and results in a direct hazard in humans' health. As mentioned, resistance to antimicrobials can decrease the effectiveness of therapeutic treatment of the disease (zoonosis) and reduce treatment's choice. Foodborne resistant strains of zoonotic bacteria may elongate the illness' duration, cause more serious illness, have a higher mortality and an increased risk of need of nursing and hospitalization, in comparison to sensitive to antibiotics strains (Mølbak, 2005).

4.2.   Indirect hazards

Antimicrobial usage in food producing animals promotes the development of antimicrobial resistance in both pathogenic and non pathogenic bacteria (Varga et al., 2009). Antimicrobial resistance genes that are carried on mobile genetic elements are likely to be transferred to human flora. This can be done by horizontal gene transfer during transit (passing) or colonization of the human body (Hunter et al., 2008). Consequently, human flora may become resistant, including harmful bacteria to humans, like nosocomial pathogen strains (Donskey, 2004). These resistance genes thereby act as an indirect hazard. (Geenen et al, 2010)

4.3.   Gene transfer from animals to humans

The main cause accountable for the dissemination of resistance genes among different species of bacteria is horizontal gene transfer (Barlow, 2009). The gastrointestinal tract has an important role and is an important place for horizontal gene transfer. This horizaontal gene transfer can be achieved interspecies and intraspecies. As *Enterococcus* spp. and *Escherichia coli* are major residents of the gastrointestinal tract of animals, they hold a wide variety of mobile genetic elements. Besides, it is shown that these bacteria act as possible donors and accepters of resistance genes (Geenen et al, 2010).

Resistance gene transfer from a donor bacterium of animal origin and a receiver bacterium of human origin has been shown, not only *in vitro* but also *in vivo* (De Niederhäusern et al., 2004; Lester et al., 2006).

4.3.1. Examples of agents

According to data availability, urgency and host-pathogen characteristics, two direct hazards and one indirect hazard were selected as examples throughout this risk profile. The selected agents are:

- *Campylobacter jejuni* quinolone-resistant (direct)
- MRSA Livestock associated (direct)
- Bacteria ESBL-producing (indirect)

4.4.   Economic consequences

Estimated costs derived from antimicrobial resistance are remarkable. Medical costs in the USA for the cure of infections caused from resistant strains in high risk hospitalized patients were evaluated. The costs ranged from 18,588$ to 29,069$ per patient and from 10.7$ to 15.0$ million for the society. (Roberts et al, 2009)

The cost to the society may be calculated as the cost of illness and should also take into consideration the costs for the detection of carriers and the isolation of them. Cost of illness comprises of direct costs of healthcare, direct costs of non-healthcare, indirect costs of healthcare, and indirect costs of non healthcare. Direct health care costs are all costs that are directly associated to prevention medicine, diagnostic tools, treatment, reconfirmation and patient care. Direct healthcare costs, for antimicrobial resistance, should also calculate the costs of screening of group of people that are at risk, costs because of positive patients' isolation, costs of working staff tested positive that are non active, costs of outbreak like surgeries and loss of hospitalization days. Direct health care costs of resistance may also be costs involved to change of empiric therapy and limitation in therapy choices. Direct non-healthcare costs are such as travel costs and time of patients, but also include expenses related to the patient's house and non official care (at home) (Geenen at al., 2010).

Other consequences of the illness and the treatment which arise are the indirect costs. Indirect costs of healthcare are the future economy on health care costs due to death at a premature age that most times are not considered (Geenen at al, 2010). Indirect non-healthcare cost consists of the worth to society of production that is lost because of the absence from work, temporarily or permanently or the longterm weakness or infirmity and the precocious mortality as a disease's consequence.

4.5.   Social consequences

Antimicrobial resistance on people's life may have severe impact in some cases but it is not thoroughly studied. Surveys on carriers and patients of Methicilin Resistant Staphylococcus aureus (MRSA) in healthcare units show that except from their somatic pain, they also suffer from mental health issues, like anxiety, depression, stigmatization or socially isolation and usually have fewer social contacts because of their fear that they are going to contaminate other people (Donaldson et al., 2007; Geenen et al, 2010).

5. Assessing the risk of the acquisition of resistant bacteria or resistance genes through the food chain

A trustworthy approach for assessing the risk to human of obtaining resistant bacteria or resistance genes via food is required. It is sure that we have a complicated task, because of the fact that there are various and many routes of adaptation. Except of the food intake, there is also the direct contact with food producing animals, pets, environmental exposure, human to human transfer etc. (See previous chapters).

In this point, we need to focalize only on the pathways of food. Exposure of human to resistant bacteria is hard to be measured quantitatively or qualitatively. Quantitative details with numbers of resistant to antibiotics bacteria in foodstuffs and details on human consumption habits are not available in all cases, and usually they are not available so as to input them into a risk assessment. It is not clear if antibiotic resistant microorganisms can live through and grow during the food-chain phases, such as processing or cooking, to a greater extent in comparison to the susceptible bacteria. In addition, in relation to the dose-response characteristics, there are limited data if antimicrobial resistant bacteria are more pathogenic or provoke more severe disorders in comparison to the non resistant equivalents. Besides, it is difficult to take into consideration the significance of transferable genes coding resistance and their indirect consequences on human health. Few risk assessments have considered this consequence, presumably due to the significant data requirements and, the scientific uncertainty connected to within host resistance gene transfer. Many different types of consumers exist, that have different consumption habits, like different type of food and different quantity of food they consume and also their susceptibility to resistant infections varies. An example could be the consumer, who could be an elderly person, an adult, a youth or an infant and within each of the above mentioned categories, might be also classified as healthy or clinically ill or immunocompromised.

A risk assessment should also consider a secondary categorization to reveal the religious and cultural condition and no compulsory dietary choices such as vegan or vegetarian. Similarly, considering the risk of exposure of farmers and their families and workers they may eat raw milk or dairy products and besides meat-workers in the

meat industry they may eat meat products. Here we can identify many types of consumers and we have to consider the potential impact of the different type of consumer on their risk of exposure (EFSA, 2008).

5.1.   Issues to be considered: risk assessment applied to antimicrobial resistance

As already mentioned, risk assessment is a tool. It may be utilized to estimate the extend of exposure and the consequent risk to human health because of certain bacteria or certain resistance type. Quantitative and qualitative risk assessments both have been used to evaluate human's health risk from resistant bacteria (Snary et al., 2004). Codex Alimentarius Commission guidelines have available accepted procedures (CAC, 1999) for microbiological food safety risk assessments and also for antibiotic resistance risk assessment. Besides, the guidelines of OIE, which are more specific to risk assessment applied to antimicrobial resistance, are also useful (OIE, 2007a).

5.1.1.   Data requirements for an antimicrobial resistance risk assessment

Which are the information required that will be determined by the risk analysis question? There is no standard data; however, previous data gaps or data deficiencies were identified and are summarized in Table 6 (Snary et al., 2004). In the following table we can see of the data requirements, gaps/deficiencies. The association between antimicrobial use of a certain antibiotic and the emergence and dissemination of antibiotic resistance is rarely known and despite many surveys have indicated that the antibiotic use is a serious factor for the development of antibiotic resistance, the correlation is non-linear. It is also defined by the way the antibiotic is consumed. In this manner, on the one side it is indicated that increased dosages may help avoiding the selection for the development of resistance to quinolone in *Salmonella* (Wiuff et al., 2003), while on the other side, repeated supplemented feeding with tylosin to chickens may cause selection for resistant to macrolide *C. jejuni*, while in contrast single treatments may seldom provoke such a condition (Lin et al., 2007).

Table 6. Data limitation and their effect on microbiological risk assessment (MRA)

Data limitation/issue	Effect on MRA
Definition of resistance – Harmonization of MIC/ disc-diffusion breakpoints required.	Data from different sources are not comparable. May limit the amount of data available for the MRA
Microbiological methods, e.g. – Selective plating v testing of one isolate from non-selective plate – Enrichment v non-enrichment – Molecular versus phenotypic methods	1. The amount of data available for the MRA may be limited if the methods are not comparable. 2. Cannot compare selective plating against the testing of one isolate without knowledge of the ratio of resistant to susceptible bacteria. 3. If enriched the number of organisms is increased and therefore cannot directly be used in the MRA
Multiple levels of the sampling framework	Large variability of sampling methods between studies. Therefore, data from different sources may not be comparable; could limit the amount of data available for the MRA.
Small sample sizes	If the sample size is small at any level of the sampling framework, the uncertainty about the associated parameter will be large. This may contribute to a large uncertainty associated with the final risk estimate.
Little data available on indicator organisms (resistant or susceptible) compared to pathogenic bacteria.	Surrogate organisms etc. may be used to overcome the data gap, thus increasing the level of uncertainty in the output of the model. This uncertainty may not be quantified.
Sensitivity and specificity of the tests used.	MRA may overestimate or underestimate the risk.
Causality unclear	Large assumptions made on the causality of antimicrobial resistance. This leads to a higher

	level of uncertainty in the model results, but which may be difficult to quantify
Lack of quantitative microbiological data	Microbial load of resistant bacteria in/on different sources is unknown, therefore either not modelled or key assumptions made.
Little information on the use of antimicrobial agents for – veterinary use (at animal and farm level) – human use	Causality is difficult to consider. May lead to a large degree of uncertainty in the results of the model.

5.1.2. Requirements for a risk assessment

The aim here is i) to identify the extent to which food serves as a source for the acquisition, by humans of antimicrobial resistant bacteria or bacteria-borne antimicrobial resistance genes; ii) to sort the identified risks and iii) to recognize possible control options for decreasing exposure. As a consequence, all agents that increase or decrease the risk of human exposure to a certain resistant microorganism from of certain origin or source would be taken into account in the wider context of the risk assessment. Concretely, the food pathways would conform the "of a farm-to-consumption" risk assessment and should have the ability to consider the variability of production systems and consumer consumption preferences between the different countries or areas.

Table 7. Category concerning antimicrobial resistance/ Category and Subcategory of food

1. Milk and dairy products (cows, goats, sheep, buffalo, horse)	1.1. Milk 1.2. Dairy products (other than cheeses) 1.3. Cheese
2. Eggs and egg products	
3. Red meats	3.1. Bovine meat and products thereof 3.2. Pig meat and products thereof 3.3. Sheep meat and products thereof 3.4. Other or mixed red meat and products thereof
4. Poultry meats	4.1. Broiler meat (*Gallus gallus*) and products thereof. 4.2. Turkey meat and products thereof. 4.3. Other or unspecified poultry meat and products thereof.
5. Aquaculture and marine	5.1. Fish and fish products. 5.2. Crustaceans, shellfish, mollusks and products thereof.
6. Vegetables, cereals, fruits	6.1. Vegetables and juices and other products thereof 6.2. Cereal products including rice and seeds/pulses (nuts, almonds). 6.3. Fruit, berries and juices and other products thereof.
7. Herbs and spices	
8. Mixed or buffet meals*	
9. Other foods*	
10. Tap water including well-	

(EFSA, 2008)

In addition, risk assessments with more details would be performed for the other sources of resistant microorganisms and would need to consider the different exposures and effects of them referred to the sub-populations of the consumers may have. Also, except for the exposure assessment, a total risk assessment should also have the need to consider the dose response need for causing infection and the clinical illness. In foodborne antimicrobial resistance risk assessment, the consequences on the outcome of infection and illness, such as treatment failure, should be included. At the end, it should also be considered the risks of direct and indirect transmission of genes within human as a host.

The number of antimicrobial classes should need to be, the bacteria of interest such as *Salmonella* spp*., Staphylococcus aureus*, *Campylobacter* spp., shiga toxin producing *Escherichia coli* and the number of potential sources, the degree of processing (raw, processed, inadequately processed). So, for the above mentioned reasons the assessment presented here is an assessment of the risk of exposure to antimicrobial resistant bacteria where food is the vehicle. As long as the assessment is designed to be qualitative, however, this is a large and complicated risk question. Therefore, a less complex approach to evaluating the extent to which food serves as a source is chosen here.

5.2. Construction of an exposure assessment template: food as a source of antimicrobial resistant bacteria.

5.2.1. Exposure pathway

The risk pathway begins, in this example, at the point of retail sale. This approach allows not including the former stages of production like farms, transport and abattoir. This approach is closer to the point of consumption of a food product. Although the pathway does not take into consideration the cross-contamination or undercooking of food, the prevalence of the resistant bacteria at the sale is used to indicate the contamination degree which becomes involved in the restaurant or the home. In this example, contamination which may occur following marketplace is not considered.

The likelihood of the presence of bacteria in food at retail and besides the probability that these bacteria present are also resistant to an antibiotic class can be combined, increasingly, to provide an overall probability of the food being contaminated with resistant microorganisms at retail. Due to the fact that data on food cross contamination and the consequences of preparedness practices of food on the viability of resistant microorganisms are rare, as well as dose-response data and consequence data, the exposure assessment stops at the point of shopping of the food at retail.

For indicator bacteria carriers of resistance genes, this template can also be used. However, the explanation of the results must consider the differences in the hazards. This applies comparing the more direct transmission of resistant pathogens (macrolide-resistant *Campylobacter*, fluoroquinolone-resistant *Salmonella*) to the more indirect risk from indicator bacteria (ESBL resistant *E. coli* and vancomycin resistant *E. faecium*) and besides the indirect risk by pathogens that carry transferable resistance genes (*Salmonella* carrying plasmid mediated ESBL resistance) where gene transfer within the human gut must also be considered. For bacteria intentionally added to food, such as fermentation bacteria, the same procedure should be applied. An integrated assessment of the consequences of exposure to genes spread horizontally would be very complex and would require not available.

Concluding, it should be mentioned that although the adoption of a simplified approach makes the risk ranking more feasible, it loses to consider the impact of control measures on the risk ranking. Therefore, the potential control options available for decreasing exposure may not be included within the risk assessment, but by using epidemiological studies or other relevant evidence (EFSA, 2008; IFA, 2015).
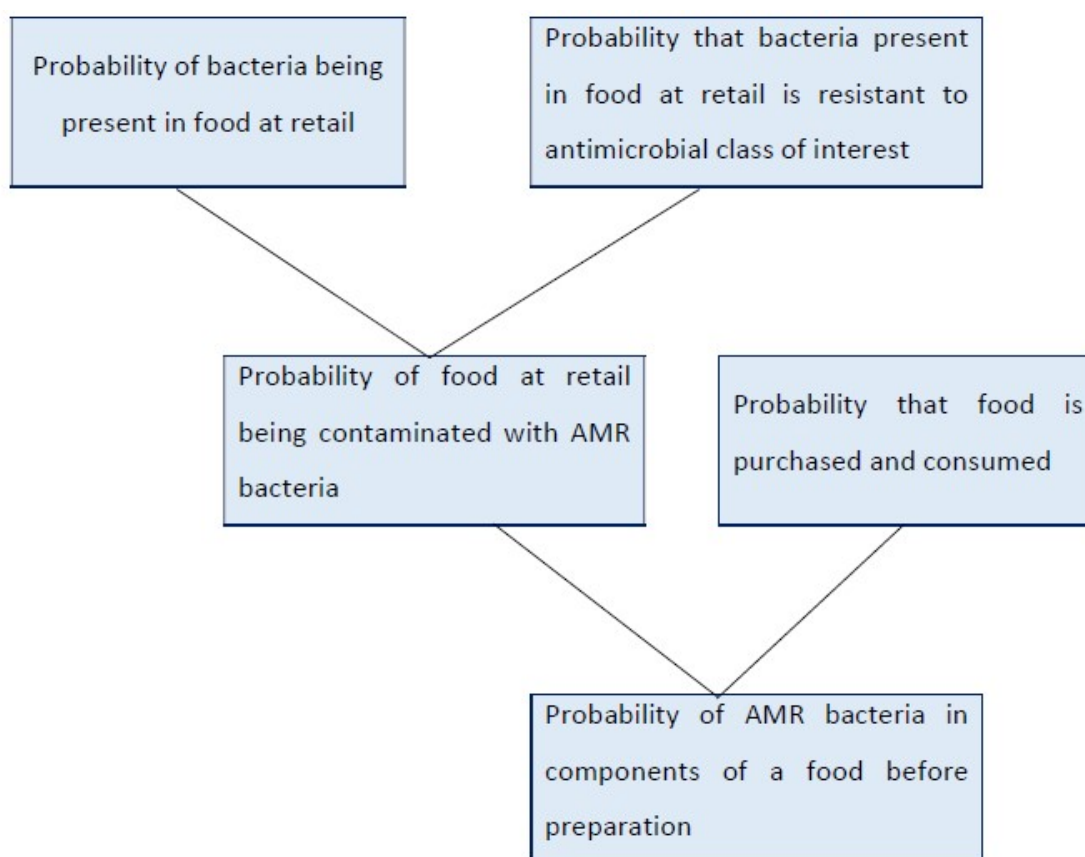
Picture 3. Example of a risk pathway for assessing the contribution of different foods to the occurrence of AMR bacteria in meal components.

5.2.2. Data requirements and availability

For each of the data requirements, the number of categories is limited to three or four, as it follows.

5.2.2.1.   Probability of bacteria being present in food at retail

Data are likely to be available for the probability of the bacteria present in food at retail, such as prevalence. However, in practice, data quantity and quality will often vary. For example, they may vary between large, retail surveys and others carried out smaller surveys where the sampling was done not randomized but by convenience. Besides, the methods followed may be different between studies and food types.

5.2.2.2.   Probability that bacteria are present in food at retail and are also resistant to antimicrobial class of interest

Antimicrobial susceptibility tests can also vary. Many studies pick one colony and test it for resistance using non selective culture plates; while others put the colony into primary isolation media containing antibiotic. This possibly affects the estimated probability of the resistant bacteria present in food. This makes it also difficult to make comparisons between studies along with the different food origin.

5.2.2.3.   Probability of antimicrobial resistant bacteria in food at retail

This probability is simply a multiplication of the two probabilities discussed above. There are three categories distinguished: high, >1%; medium, 0.01 - 1 %; low <0.01%.

5.2.2.4.   Probability that food is purchased and prepared for consumption

The probability of the food being purchased and consumed can be obtained from consumption studies, that vary in the level of detail output, different designed purpose (nutritional rather than food safety issues). The diverse range of food stuff, the different levels of processing must be considered as this affects the risk of the consumer exposed to the hazard (consumption data to the level of raw, minimally processed and processed).

6. Policy overview

At the international, EU and IS levels, notable policy instruments already exist to tackle AMR in, but they are not adequate in addressing the increasing problem of antimicrobial resistant bacteria, that are spreading in the environment. Healthcare sector should play a primary role in the fight against AMR. Hospitals and health systems can take an extensive approach to diminish AMR in humans and the environment. This can be achieved by supporting actions that encourage medical professionals to safely minimize antibiotic prescription and follow food policies healthy and sustainable (Maghear et al. 2017).

6.1. International level

Antibiotic resistance is worldwide problem due to human mobility and trade of food and animals; it is a problem that crosses national borders. Antibiotics' overuse and as consequent antibiotic resistance in one region will frustrate achievements in AMR elsewhere (Nathan and Cars, 2014). For that purpose, countries must focus to the spread of AMR and international and collaborative action is needed.

In 2009 the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established, for future collaborations between the U.S. and the EU as to increase information exchange, understand new practices and best approaches, as well as develop premier relationships (CDC, 2016). To deal with the challenge of antimicrobial resistance at the international level and to achieve the goal settings of the Global Action Plan on Antimicrobial Resistance, the World Health Organization in collaboration with the Food and Agriculture Organization and the World Organization for Animal Health, has published multiple global strategies for antimicrobial resistance (AMR). This Global Action Plan aims to ensure the continuity of the ability to treat and prevent infectious diseases with the use of effective and safe medicines. WHO has also created and continues to update, a list of medically important antibiotics, to manage the arising risk from antibiotic use in agriculture. Besides, WHO provides guidance on surveillance of antibiotic resistance and antibiotic use (WHO, 2017; WHO, 2018).

The OIE has also lots of activities linked to antimicrobial resistance. A global survey of veterinary antibiotics use and a list of sales of antibiotics important for animal agriculture (OIE, 2015; OIE, 2018). Other OIE surveys are available online for: i) improving general and political awareness of AMR, ii) promoting better practices in food and agricultural systems, and iii) ensuring judicious use of antibiotics to help battle AMR (Maghear et al, 2009. According to the FAO's Code of Practice to Minimize and Contain Antimicrobial Resistance, this risk management will be performed with respect of a 'One Health Approach' (FAO, 2005). This Code of Practice focuses on antimicrobial use in food animals and recognizes that antimicrobial resistance is also an ecological problem. The One Health concept is an approach implementing policies, programs, research and legislation, in which different and multiple sectors work together and collaborate to achieve better public health outcomes (WHO, 2017b).

6.2. European Union level; the role of EFSA in AMR

The European Food Safety Authority (EFSA) is an agency funded by the EU that acts as scientific advice and communication source on risks related to the food chain. EFSA is actively involved in several activities within the space of antimicrobial resistance (AMR). It provides scientific recommendation used to support the European legislator and Member States in creating effective and timely risk management choices in tackling AMR for example, in reducing the need to use antimicrobials in food-producing animals or in managing emerging threats such as resistance of bacteria to beta-lactams, colistin and carbapenems. EFSA provides advice on how to monitor antimicrobial resistance in food and food animals and gathers and analyzes data collected at the national level in Europe. Finally, it actively communicates the risks connected to antimicrobial resistance.

6.2.1. <u>Scientific advice to the risk manager; scientific advice and AMR risk assessments</u>

EFSA is providing with scientific and technical advice on AMR regulators, as a basis of informing related risk management decisions. Over recent years, EFSA has been consulted by the European Commission on a variety of topics and has taken the initiative to analyze and investigate AMR related emerging risks of particular concern

for food safety and public health. For instance, scientific opinions were adopted by the EFSA Panel on Biological Hazards (BIOHAZ Panel) on MRSA (EFSA, 2009), ESBL-/AmpC producing and carbapenemase-producing bacteria in food animals and food (EFSA, 2011; EFSA, 2013). The AMR data collected may additionally be useful once investigating the effectiveness of management measures taken or the final impact of an AMR local / national action plan and efforts towards the reduction of AMC and AMR in both humans and. Animals.

7. How can we act now?

The magnitude of the matter is currently accepted. Even today, 700,000 individuals die of resistant infections each year. We tend to estimate that by 2050, ten million lives a year and an additive one hundred trillion USD of economic output are in danger because of the increase of drug resistant infections, if we tend not to realize proactive solutions currently to block the increase of drug resistance. Antibiotics are a special class of antimicrobial medicine that underpins modern medication as we all known: if they lose their effectiveness, key medical procedures (such as gut surgery, caesarean sections, joint replacements, and therapy that depress the immune system, like chemotherapy) might become too dangerous to perform. Most of the direct and far of the indirect impact of AMR can fall on low and middle-income countries.

To stop the worldwide rise of drug-resistant infections, there's a demand issue that must be mounted. The supply of latest medicines is lean to stay up with the rise in drug resistance as older medicines are used a lot of wide and microbes evolved to resist them. At the identical time, the demand for these medicines is incredibly badly managed: huge quantities of antimicrobials, specifically antibiotics, are wasted globally on patients and animals. A change is needed within the manner that antibiotics are consumed and prescribed, to preserve the quality of existing drugs for extended and to scale back the urgency of discovering new ones. Governments ought to be control responsible on this goal to scale back the demand for antimicrobials and specifically antibiotics, as ought to the most sectors that drive antibiotic consumption: aid systems, the pharmaceutical companies and also the farming and food production industry.

The main steps to reduce demand are the following:

1. *A worldwide public awareness campaign*. We need to boost world awareness of AMR across the board, so patients and farmers don't demand, and clinicians and veterinarians do not prescribe antibiotics once they are not required. So, policy manufacturers make sure that policies to tackle AMR are taken forward. The value of running a sustained public awareness campaign across the globe would

depend upon its nature and scope. Based on estimates it might cost between forty and one hundred million USD a year.

2. *Improving hygiene and sanitation and prevent the spread of bacteria.* Improving hygiene and sanitation was essential in the 19th century to counter infectious diseases. Two centuries later, this is often still true and is additionally crucial to reducing the increase in drug resistance: the fewer individuals get infected, the less they have to use medicines like antibiotics, and also the less drug resistance arises. All countries have to act. Some within the developing world can have to specialize in rising the fundamentals 1st, by increasing access to wash water and sanitation. For alternative countries the main target are to scale back infections in health and care settings, like limiting superbugs in hospitals. The best manner that each one people will facilitate counter the spread of infections is by correct hand washing.

3. *Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment.* In agriculture and aquaculture, there are circumstances where antibiotics are required to maintain animal welfare and food security. However, very often their global use is not for treating sick animals, but rather to forestall infections or just as growth promoters. The quantity of antibiotics used in livestock is large. In the US, for instance, of the antibiotics outlined as medically vital for humans by the North American nation Food and Drug Administration (FDA), over 70 % (by weight) are sold-out to be used in animals. Several countries are possible to use a lot of antibiotics in agriculture than in humans, however they do not publish the data. Most of scientists see this as a threat to human health, on condition that wide-scale use of antibiotics encourages the problem of resistance, which might unfold to have an effect on humans and animals alike. We tend to propose three steps to boost this case. First, 10-year targets to scale back supererogatory antibiotic use in agriculture, introduced in 2018 with milestones to support progress according to countries' economic development. For this to succeed, governments should support and speed up current efforts, as well as those of the globe Organization for Animal Health (OIE) et al., to live antibiotic use and farming practices. Second, restrictions on bound kinds of critically important antibiotics. Several antibiotics

that are currently last-line in medicine for humans are getting used in agriculture; action ought to be taken on this desperately by a world panel. Third, we have to improve transparency from food producers on the antibiotics used to raise the meat that we eat, to modify consumers to create more informed purchase selections. Antibiotics will reach the environment in various ways like through sewage systems (also from hospitals) and run-off from food-producing units like farms and may then create potential issues for AMR. One area that has not received enough focus thus far is the way that the active ingredients for antibiotics are manufactured and notably the impact of effluent from factories on AMR in close water systems. (supply chains). To tackle this, we need regulators to line minimum standards for the treatment and release of producing waste; and also manufactures to drive higher standards through their supply chains. Both of them should take responsibility and proper this supererogatory environmental pollution straightaway.

4. *Improve worldwide surveillance of antimicrobial resistance and anibiotic consumption in humans and animals.* Surveillance is one amongst the cornerstones of infectious disease management, nonetheless, has till recently been typically ignored and remains under-resourced within the fight against AMR. After Ebola, countries have begun to increase funding during this area recently, specifically the US Government via the Global Health Security Agenda (GHSA), the United Kingdom government with its announcement last years of the 375 million USD Fleming Fund and also the World Health Organization (WHO) with its developing Global AMR Surveillance System (GLASS). With oversight from the WHO, governments should build on these efforts to collect data about the consumption of antimicrobials, the levels of resistance, and the underlying biological reasons for resistance, supporting countries that need it most in doing so. They must also put systems in place now that will make the most out of the 'big data' on drug resistance that will be generated on an unprecedented scale as diagnostic tools are modernized, and cloud computing is embraced.

5. *Promote rapid new diagnostics to reduce unnecessary use of antimicrobials.* Rapid diagnostics could transform the way we use antimicrobials in humans

and animals: reducing unnecessary use, slowing AMR and so making existing drugs last longer. It is not acceptable that much of the technology used to inform the prescription of important medicines like antibiotics has not evolved substantially in more than 140 years. Rich countries must lead the way to change this: they should make it mandatory that by 2020 the prescription of antibiotics will need to be informed by data and testing technology wherever available and effective in informing the doctor's judgement to prescribe. This will spur investment by giving diagnostics developers the assurance that effective tests will be used. Our proposed Global Innovation Fund for AMR would support early-stage research in this area. In low and middle-income countries where access and affordability are the main barriers, a diagnostic market stimulus would provide top-up payments when diagnostics are purchased, in a similar way that setting up Gavi, the Vaccine Alliance, in the early 2000's revolutionized global vaccine coverage in what was one of the best returns on investment to support economic development and wellbeing.

6. *Promote development of vaccines and alternatives.* Vaccines can prevent infections and therefore lower the demand for therapeutic treatments, reducing use of antimicrobials and so slowing the rise of drug resistance.

8. Conclusions

Microbiological risk assessments mostly focus on evaluating human adverse health risks from exposures to pathogenic microorganisms. Risk assessment is a decision tool that gives risk managers an objective picture of what is known at a particular time. Limited access to all relevant information or lack of data make risk assessments more difficult. What is known at a certain time is not sufficient for a risk manager in the selection of a strategy. When the criteria of a risk manager for making a decision are well defined; a risk assessment based on current information provides guidance to make the choice of a correct decision.

Foodborne antimicrobial resistance risk assessment is a process to evaluate qualitatively or quantitatively the health risks after exposure to resistant to antibiotics bacteria or resistance genes, in the food pathway. Hazard could be a resistant bacterium as well as a resistance gene in the food chain. Foodborne antimicrobial resistance is addressed either as a direct or an indirect hazard, through resistance transfer. The direct hazard is the presence in food of resistant to antibiotics pathogenic bacteria which have the ability to colonize or infect a human, after ingestion of the food, or as a hazard that arises through handling contaminated food and the person acquires an infection. Indirect hazard happens when a bacterium resistant to antibiotics may transfer resistance genes to a bacterium pathogenic for humans, directly, or via another commensal bacterium. In this case, the hazard is the resistance gene.

Antimicrobial resistance has increased in bacterial pathogens worldwide leading to treatment failures in human infectious diseases. Resistance pathogenic bacteria are of major concern. Bacteria are able to adapt speedily to new environmental conditions like the presence of antibiotic molecules and consequently antimicrobial resistance may occur with increasing exposure to antimicrobials. Major concerns about antibiotic resistance in bacteria isolated not only from hospitals, but also from community and food products, have been raised at national but also at international levels.

As an effort to battle with the complexity of resistance selection, the transfer through the food chain, and the consequences in human's health, risk assessments are now being applied. Risk assessments have been conducted for many antibiotics used in food producing animals and the estimated risk to human health is determined. Risk management strategies implemented to minimize antibiotic resistant foodborne bacteria along the food chain must be improved. These new strategies must include the use of drugs alternatives to antibiotics, implementation of prudent use of antibiotics and implementation of national antimicrobial resistance monitoring programs.

Although nowadays we have much emerging knowledge about antimicrobial resistance and will definitely help us built improved quantitative or qualitative antimicrobial resistance risk assessments, the immediate need is to characterize the health consequences on human health from foodborne antimicrobial resistance, according to the author. Steps taken by Public health and food sectors and also by research groups toward improved data for risk assessments include the development of epidemiological surveillance networks (NARMS, EFSA/ECDC/EMA). In the past databases reported large-scale epidemiological findings on resistant strains and resistance frequencies. Other data are needed to improve estimation for resistance reservoirs that may occur in the food pathway. Nowadays, the interest of public health agencies in the impact of risk management strategies in reducing antimicrobial resistance has fostered development of surveillance databases. This is absolutely necessary, due to the fact that even today, 700,000 individuals die of resistant infections each year. We tend to estimate that by 2050, ten million lives a year and an additive one hundred trillion USD of economic output are in danger because of the increase of drug resistant infections, if we tend not to realize proactive solutions currently to block the increase of drug resistance. Besides, the estimated costs of antimicrobial resistance are considerable. Calculated medical costs in the USA for the cure of infections with antimicrobial resistant strains in high-risk hospitalized patients ranged from $18,588 to $29,069 per patient. In parallel, social consequences on everyday people's life may also be severe. Studies on patients and carriers in healthcare units show that except from their somatic pain, they also suffered from

psychological problems, such as anxiety, depression, stigmatization due to the fear of contaminating people.

These are the trends. Everyone has to think how he can act today!

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