TAFS

TRUST IN ANIMALS AND FOOD SAFETY

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TAFS White Paper

Usage of antimicrobials in animal farming

What we know about the risks and what we should know

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1. Executive summary

Along with the intensification of animal production, the risk of infectious diseases has also increased, leading to higher usage of antimicrobials for treatments and prevention worldwide. When antimicrobial substances are used, bacteria will adapt to survive and often become resistant. Food derived from animals is bound to carry bacteria, an increasing proportion of which is likely to harbor resistance genes. The latter can then be passed on to other bacteria, but the detailed effect in complex bacterial populations, for example in the human gut, is not yet known. The pathways connecting animals, food and the environment and allowing for the transfer of resistant bacteria are diverse and not well understood. Particularly, knowledge of the role of bacteria in the environment, e.g. soil or water, as a reservoir of resistance is lacking. Only a few studies provide all elements needed for causal proof that antimicrobial usage in food animals and resistance in humans are linked. Yet, new laboratory methods now allow for the efficient analysis and comparison of entire bacterial populations and should – if used in combination with epidemiological reasoning – help provide important information to fill many current knowledge gaps in the coming years.

Some food-borne bacteria can cause diseases in humans which – as a consequence of resistance – can become more difficult to treat. Other bacteria are more relevant in the context of food spoilage. A number of processing technologies are used to reduce bacterial spoilage on food. With the exception of heat treatment, the specific effectiveness of processing technologies for resistant bacteria has not yet been established. Another option for interrupting the propagation of bacteria within the food chain is the use of microbicides. Although their effectiveness is currently not disputed if applied properly, the risk of resistance has not been studied systematically.

When consuming food, the exposure to bacteria (dead or alive) is practically inevitable. The fate of resistance genes during digestion is currently unknown. If resistant bacteria survive digestion and cause disease, this can lead to treatment failure if antibiotics are required. Resistance genes can also be transferred to other gut bacteria, but the frequency and relevance of such exchange is currently unknown.

To conserve the efficacy of antibiotics, their use is regulated in terms of registration, sale, indication and dosage. Usage statistics are not yet compiled in all countries, but where available, they indicate that a very large proportion is sold for non-human use, mainly pigs and poultry. Usage restrictions for livestock were implemented by some countries, but the effectiveness of such measures is currently fully documented for only a few examples. Livestock production without antibiotics is currently pursued by very few producer groups and processors, while most other industry operators promote so-called prudent use guidelines as well as other measures that generally aim to increase the health of food animals, e.g. by biosecurity, hygiene or vaccination. The food animal veterinarian has a documented role as a key expert and advisor for prudent usage to help select the measures that are most appropriate and effective for a specific farm.

At present, many pieces of the puzzle describing the complex relationships and dynamics in the resistance ecosystem remain unknown, but substantial ongoing research efforts should be able to fill some of these gaps in the coming years. Answers are lacking to three main questions:

(1) what is the extent of antimicrobial resistance occurrence, spread and public health impact?

(2) which factors are most influential for antimicrobial resistance occurrence and therefore relevant for control?

(3) what are the costs and benefits of control measures?

Policies against antimicrobial resistance should be evidence-based. Also, any intervention will come at a cost. Therefore, the benefits for public health need to be balanced against the impact of restricted use on agricultural productivity, animal welfare and food security.

2. Introduction

The increasing demand for animal-derived food has led to an intensification of animal farming in most countries in the developed world. In such industrialized husbandry systems, large numbers of animals are housed closely together which intensifies the infection pressure for many diseases. This has led to an increased use of antimicrobials[1]. Antimicrobials are used to treat infectious diseases in both animals and in humans. The resistance that results from antimicrobial usage is increasingly discussed as a risk to public health. The World Health Organization (WHO) and many other regional and national agencies are highlighting the consequences of non-human usage, i.e. the use in agriculture, and specifically the risks for public health. The main concern is that treatment of certain human infections will no longer be possible due to antimicrobial resistance. A list of substances seen as critically important for public health has been defined. The WHO argues that their usage in animals should be limited or discontinued[2,3].

In order to understand this ongoing debate, the biological dynamics and the complex risk factors driving antimicrobial resistance have to be considered[4]. It is the objective of this article to summarize the current scientific evidence. Although resistant bacteria also occur in the environment, our primary focus is on the food chain, and mainly on animal-derived food. The importance of other risk pathways such as the transfer of resistant bacteria from animals to humans by direct contact – for example from pets – are acknowledged but not within the scope of this paper. To explain the risks of antimicrobial resistance, we first consider the general role of bacteria in food, then why antimicrobials are used and finally how they affect consumers and impact on health.

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[1] In this article, "antimicrobials" are defined narrowly to encompass antibiotics and antibacterial agents but not antivirals and anti-parasitics. This is consistent with the terminology used by the European Commission (e.g. Commission Notice 2015/C 299/04), the European Food Safety Agency (EFSA) and also the European Centre for Disease Control (ECDC) and the Scientific Committee on Emerging and Newly Identified Health Risks.

[2] WHO (2001). Global strategy for containment of antimicrobial resistance. Geneva, 105 pp. www.who.int

[3] WHO (2011). Critically important antimicrobials for human medicine. 3rd Revision. Geneva, 23 pp.

[4] Chang, Q., Wang, W., Regev-Yochay, G., Lipsitch, M., & Hanage, W. P. (2015). Antibiotics in agriculture and the risk to human health: how worried should we be? *Evolutionary Applications*, *8*(3), 240–247. doi:10.1111/eva.12185

3. *Why do bacteria occur in food?*

Bacteria are present almost anywhere in the environment. Even under the most extreme conditions, for example, glacier ice, there is microscopic life that is well-adapted to survive under very extreme conditions. Bacterial survival mainly depends on temperature, availability of oxygen[5], humidity and acidity. Bacteria are present in surface water, in the soil and even in the air. It is therefore not surprising that almost any food will carry bacteria. The origin of such bacteria is diverse depending on the type of food. For example, food grown in the field will mostly carry bacteria found in soil and in fertilizers. Food that originates from animals, for example milk, will carry bacteria found in or on these animals and their environment. Some bacteria are also intentionally added to food for processing, for example for fermentation (examples are yoghurt or salami).

In the human (and animal) body, bacteria are commonly found on the skin and in the intestines. These bacteria are not causing disease, but help digest food or live off substances excreted by our bodies. Such bacteria are called “commensals”. They have an important role in maintaining the normal functioning of our bodies. The nature of our own bacterial ecosystems has not yet been well researched, but recent results indicate that the type of food we eat is an important factor determining the composition of the gut microflora. Interestingly, it even looks like we may all have our own individual “bacterial fingerprint” [6, 7].

In addition to these “normal” bacteria, food may contain bacteria that cause illness in humans, so-called pathogens. These are unwanted and many steps are taken in order to prevent them from contaminating food and to stop or delay their survival and growth on food. Hygiene is essential when harvesting food that is perishable, i.e. prone to spoilage due to bacteria. Simple preservation methods include cooling (i.e. making it too cold for bacteria to grow), salting, curing and drying (all reducing

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[5] Or absence of oxygen, depending on the bacteria species.

[6] Schloissnig, S., Arumugam, M., Sunagawa, S., et al. (2013). Genomic variation landscape of the human gut microbiome. *Nature*, *493*(7430), 45–50. doi:10.1038/nature11711

[7] Raymond, F., Ouameur, A. A., Déraspe, M., et al. (2015). The initial state of the human gut microbiome determines its reshaping by antibiotics. *The ISME Journal*, 1–14. doi:10.1038/ismej.2015.148

the available water that is required for bacterial growth). Heat is also an effective measure for conserving food as it can kill bacteria. Such measures are effective as long as there is no re-contamination. However, none of these measures is perfect so all food will eventually spoil and no longer be edible.

Pathogenic bacteria are of particular relevance when considering animal-derived foods such as meat, milk and eggs. The most commonly known pathogens are *Salmonella* and *Campylobacter*, but verotoxin-producing *Escherichia coli*, *Listeria monocytogenes*, Mycobacteria, *Yersinia enterocolitica* and *Brucella* are also commonly transmitted by food in certain regions. As most of these bacteria can make humans ill, food should only be harvested from healthy animals[8]. However, there are also bacteria that do not affect animals but only cause disease in humans. As there is no easy indication of which animals carry such bacteria, it is more difficult to prevent them from entering the food chain and reaching consumers. Substantial control programs are therefore ongoing in many countries to reduce the risk of human exposure to such agents via animal-derived food.

4. Why and how do we use antimicrobials

As bacteria can make animals and people ill, we use antimicrobials for treatment. Antimicrobials are substances with a wide range of chemical structures that are able to kill bacteria. Some antimicrobial substances occur in nature and others were created by pharmacists. Thanks to antimicrobials, many diseases that used to be lethal are now readily treated, for example bacterial pneumonia. This is true for both humans and animals.

It is not surprising that the ability of bacteria to resist antibiotics has also been evolving over time. Regardless of which type of antibiotic you use, due to the large numbers of bacteria in a population, it

[8] Pathogens can also occur on plants or contaminate vegetal food and cause human disease. An example for this is the large outbreak of foodborne illness in Europe in 2011 which was caused by toxin-producing *E. coli* on sprouts.

is likely that some will be able to survive due to their diversity of genetic makeup (presence of resistance genes). As all bacteria that lack resistance genes will die, antimicrobial use will inevitably lead to the selection of resistant bacteria. Such resistant bacteria have a competitive advantage and will outgrow others in an environment where antibiotics are present[9]. The ability to survive exposure to antimicrobials can be passed on from one generation of bacteria to the next (so-called “vertical resistance transfer”)[10]. An alternative mechanism exists when the genetic information for resistance is located on mobile genetic elements that can be passed between bacteria of the same species or between different species (so-called “horizontal resistance transfer”). The latter is estimated to be the more relevant mechanism of resistance transfer. It is also of particular concern because it facilitates the spread of resistance traits between different bacterial species. When bacteria are stressed, for example by harsh environmental conditions, such transfer can be enhanced. Bacteria are stressed when antibiotics are used in concentrations of substances that allow some survival. The detailed extent and dynamics of changes in bacterial populations in animals after antimicrobial treatment is not known. First results using novel research methods including next generation sequencing in humans indicate that the changes are complex and that there is substantial variation between individual patients. Also, some changes appear to be relatively short-lived.

As resistance to antibiotic substances is inevitable, the key goal is to preserve susceptibility as long as possible. To achieve this, usage is regulated, including legislation for licensing, sale and restricted access (prescription-only) to antibiotics. However, adulterated antimicrobial products are known to circulate widely for use in both animals and humans. The risk of resistance development is higher if the dosage is not right (typically too low and/or too short) or the antimicrobial is not appropriate for the specific pathogen involved. It is therefore part of the so-called prudent use principles to use laboratory diagnostics and to apply antimicrobials correctly. In animals, antimicrobial treatment can

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[9] Also, they can be disadvantaged in an environment where no antibiotics are present as their general fitness and ability to compete against bacteria without resistance traits tends to be reduced.

[10] Rodríguez-Rojas, A., Rodríguez-Beltrán, J., Couce, A., et al. (2013). Antibiotics and antibiotic resistance: A bitter fight against evolution. *International Journal of Medical Microbiology*, *303*(6-7), 293–297. doi:10.1016/j.ijmm.2013.02.004

target individuals or groups. The latter can be administered via food or water. Individual treatment is preferable as it is more targeted. Prudent use guidelines (sometimes also referred to as “stewardship programs”) have been developed for antimicrobial usage in food animals as well as for pets. The effectiveness of such programs was demonstrated in health care settings.

In order to better understand the link between the use of antibiotics in food animals and the risk for consumers, statistics are required on how much and which antibiotics are used in which agricultural sector. Many countries therefore make it compulsory for all treatments to be registered. International comparisons are facilitated by the increasing use of harmonized ways of collecting and analyzing data on antimicrobial usage in both animals and humans. However, major gaps still remain in terms of the extent and level of detail of data recording[11]. Some countries know the amount of antimicrobial used on every individual farm while others only know how much is traded in a country or sector as a whole. The latter provides insufficient detail to inform measures for reducing usage. From countries that do have detailed statistics, it is reported that up to 80% of total antimicrobials sold are used in food animals. The pig and poultry sectors tend to be the major users in agriculture.

Apart from treating disease, antibiotics are also used as growth promoters in animal production. This means that a low dosage is used as a feed additive for healthy animals. As this practice increases the risk of resistance development, it was abandoned in many countries in the interest of preserving the effectiveness of antibiotics for public health[12]. Where growth promoters are still allowed, they are estimated to account for 60-80% of usage in animals. Antibiotics or classes of antibiotics that are used in human medicine can be administered to food animals in the form of free-choice medicated feeds (FCMF), where animals choose how much feed to consume. Routine administration of these drugs to livestock has been widespread which has selected for microorganisms that are resistant to the same

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[11] Garcia-Migura, L., Hendriksen, R. S., Fraile, L., & Aarestrup, F. M. (2014). Antimicrobial resistance of zoonotic and commensal bacteria in Europe: The missing link between consumption and resistance in veterinary medicine. *Veterinary Microbiology*, *170*(1-2), 1–9. doi:10.1016/j.vetmic.2014.01.013

[12] Jensen, H. H., & Hayes, D. J. (2014). Impact of Denmark’s ban on antimicrobials for growth promotion. *Current Opinion in Microbiology*, *19*, 30–6. doi:10.1016/j.mib.2014.05.020

antibiotics[13]. Antibiotics are also used in plant production, e.g. to control bacteria affecting fruit trees. Such practices have come under increasing scrutiny because of the risk of resistance development in bacteria that could reach consumers. For example, the WHO calls for a global ban of the use of antibiotics as growth promoters, but many countries have not yet adopted the required legislation.

5. How do antimicrobials or resistant bacteria reach consumers via food?

The use of antimicrobials in food production can have two types of undesired effects: it can lead to antibiotic residues, and it can lead to the development of resistance in bacteria. The former is generally straightforward to prevent by adhering to dosage regulations and withdrawal times that are defined as part of the licensing process for each antimicrobial. The focus is therefore on the latter issue.

Antibiotic resistance is a characteristic of a bacterium, and bacteria are present in or on almost any food. In order to understand the dynamics and spread of resistance, we therefore need to understand the pathways that connect animals, plants and the environment and their respective (susceptible or resistant) bacteria populations with people via food[14]. Some pathways are simple and quite direct, for example resistance in a commensal bacterium on meat or resistance in fecal bacteria that are contaminating vegetables. These resistant bacteria may be directly ingested by consumers. Other pathways are indirect, for example resistance in a fish-specific bacterium, the genetic information for which can be passed on to commensals or other (non-fish) bacteria which in turn are causing disease in humans. Due to the diversity and complexity of food items, their range of origins and the – often international – trade channels, there is a complex network of pathways for food items as well as the bacteria in or on them. At present, we only have a patchy understanding of how such pathways are linking animals (and the use of antimicrobials to treat them) with consumers. Some studies have

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[13] Love, D.C., Davis M.F., Bassett A., Gunther A., Nachman K.E. (2011) Dose imprecision and resistance: free-choice medicated feeds in industrial food animal production in the United States. *Environ Health Perspectives 119*(3), 279-283.
[14] Verraes, C., Van Boxstael, S., Van Meervenne, et al. (2013). Antimicrobial resistance in the food chain: a review. *International Journal of Environmental Research and Public Health, 10*(7), 2643–69. doi:10.3390/ijerph10072643

provided all elements of the causal proof by showing that resistance in humans was reduced in response of discontinued use of specific substances in food animals. However, for other substances the impact of reduced use was less than expected.

In particular, aspects of indirect pathways such as the spread of resistant bacteria and genes through slurry and waste water are not well understood. Resistance among soil bacteria is common, but can be due to naturally occurring antimicrobials. In fact it can be argued that antimicrobial production and resistance evolution is an ancient process that has been ongoing for thousands of years in the soil, and that resistance due to human activities is only a recent event. Many environmental bacteria cannot be cultivated in the lab so their resistance mechanisms remain unknown. Reviews of the current literature indicate that the occurrence of resistant bacteria is higher in the vicinity of livestock farms. Also, some resistance genes of soil bacteria were found to be identical to genes in bacteria from clinical samples, suggesting a very high probability of transfer of genetic material to soil bacteria[15]. However, there is a need for more rigorous design of studies in order to be able to quantify the role of this pathway. It is known that particularly mobile resistance genes are common in soil bacteria, and it is probable that they provide an important reservoir for resistance. Another complex environment is waste water which can contain high amounts of discarded or eliminated antimicrobials from patients – both human and animal. Such residues are not always fully removed by wastewater treatment. Environmental bacteria exposed to such residues may develop resistance and pass it on within the ecosystem[16]. Novel research methods that allow the analysis of the genetic information for resistance in entire bacteria populations (thus describing the so-called "resistome") will facilitate research in this field. First evidence confirms that identical resistance genes can be found in soil bacteria, gut microflora and human pathogens. A number of substantial research projects are ongoing in different countries using such tools to

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[15] Cantas, L., Shah, S. Q. A., Cavaco, L. M., et al. (2013). A brief multi-disciplinary review on antimicrobial resistance in medicine and its linkage to the global environmental microbiota. *Frontiers in Microbiology, 4,* 96. doi:10.3389/fmicb.2013.00096

[16] Huijbers, P. M. C., Blaak, H., de Jong, M. C. M., et al. (2015). Role of the Environment in the Transmission of Antimicrobial Resistance to Humans: A Review. *Environmental Science & Technology*, 150928162511004. doi:10.1021/acs.est.5b02566

investigate the spread of resistant bacteria and/or resistance genes in the environment as well as along the food chain.

Bacteriophages are viruses that infect bacteria[17, 18]. The number of phages present in animal-derived food is not well quantified but likely to be large, as indicated by recent studies conducted in poultry meat. The latter study also showed that >10% of the chicken meat samples included phages with at least one but often several resistance genes. The release of phages can be favored by antimicrobial treatment and the related destruction of bacterial cells thus enhancing the spread of resistance genes. Phages are also considered to control bacterial carriage in food animals. Consequences of such practices in terms of the spread of resistance genes need further attention.

Food processing and preservation methods are used to ensure the safety and/or extend the shelf-life of foods by reducing bacterial load or reducing pathogens to an acceptable level. A wide range of processing technologies is used, including heat treatment, preservation and processes considered as minimal processing. Application of validated heat treatment during food processing is intended to eliminate or reduce the amount of live bacterial cells and inactivate pathogens (e.g. pasteurization of milk). Carcass washes with hot water and steam treatments with incorporation of active agents such as nisin and GRAS substances are applied with the same objective[16]. Current knowledge indicates that foodborne antibiotic resistant bacteria, including foodborne pathogens, are as susceptible to heat treatment as non-resistant counterparts.

Minimal food processing technologies (e.g. use of salt or acid, drying, refrigeration, controlled atmosphere packaging, etc.) do not necessarily kill bacteria, but ensure food safety and quality by preventing the growth of the bacteria. In general, several of these (minimal) processing steps are applied consecutively – the multiple hurdle approach which is a valid concept applied in the food industry around the globe to control bacterial growth[17]. It is possible that a stress response will be

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[17] Phage-mediated gene transfer is called “transduction”.
[18] http://www.fda.gov/animalveterinary/products/animalfoodfeeds/generallyrecognizedassafegrasnotifications/ucm192224.htm

triggered in bacteria exposed to these sub-lethal treatments which may predispose them to exhibit increased antimicrobial resistance (or co-resistance). The number of studies investigating such phenomena is limited. Also, effects may be transient. Results are therefore currently not considered sufficient to draw conclusions. Differences in survival rates for other preservation processes remains largely unexplored but is considered unlikely.

Resistant bacteria and resistance genes present in unprocessed (raw) food can be ingested but also, they can be transferred to other food during food handling and preparation. The extent of such cross-contamination depends on the general hygiene standards that are applied. Transfer of bacteria is possible via hands and also via kitchen utensils such as cutting boards or knives, but the transfer is likely to be less than 1% of the original amount of contamination.

Transmission of bacteria along the food chain can also be interrupted by the use of antimicrobial agents (biocides), i.e. chemical substances that are used to destroy microorganisms during food processing, but also in healthcare and other settings. These include preservatives, disinfectants and sanitizing agents that are used to reduce bacterial load. Resistance to microbicides has been observed[19,20], but the details of possible genetic responses and a link to antimicrobial resistance are yet unknown. Some difference in susceptibility between resistant and non-resistant strains was found with respect to biocides, but no consistent pattern could be detected and results remain limited because tests were mainly conducted under laboratory conditions. If applied properly, biocides such as disinfectants are largely effective. However, there are indications of co-resistance against biocides and certain antibiotics, particularly if substances are not used at a sufficient concentration.

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[19] http://link.springer.com/chapter/10.1007%2F978-1-4615-2105-1_1#page-1

[19] Giuliano, C. A., & Rybak, M. J. (2015). Efficacy of Triclosan as an Antimicrobial Hand Soap and Its Potential Impact on Antimicrobial Resistance: A Focused Review. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *35*(3), 328–336. doi:10.1002/phar.1553

[20] Maillard, J. Y., Bloomfield, S., Coelho, J. R., et al. (2013). Does microbicide use in consumer products promote antimicrobial resistance? A critical review and recommendations for a cohesive approach to risk assessment. *Microbial Drug Resistance-Mechanisms Epidemiology And Disease*, *19*(5), 344–354. doi:10.1089/mdr.2013.0039

The selling of food containing resistance genes is currently not regulated. Regulations only define the extent to which food can contain pathogenic or non-pathogenic bacteria, some of which may carry resistance genes. As sterile food is not feasible – nor desirable – there is no zero-tolerance for bacterial contamination (with very few exceptions[21]). Similarly, there are no regulations in place at the moment that would restrict the trade of food contaminated with bacteria harboring resistance genes. Recently, some countries were considering restrictions in relation to the spread of a resistant pathogen known to cause hospital infections, namely methicillin-resistant *Staphylococcus aureus* (MRSA). However, due to parallel non-food-related exposure pathways and due to the rapid spread of the strain, no measures were eventually taken for food or food animals.

6. *What are the consequences for food consumers?*

Food can be ingested raw (unprocessed), minimally processed or processed. These processes are designed to inactivate pathogens and extend the shelf-life of the product by preventing bacterial spoilage. Depending on the type and level of processing of a food product, when consumed, we are inevitably ingesting bacteria (dead and alive) as well as bacterial genetic material. Dead bacterial cells may remain intact and their genetic material – including genes encoding resistance – might be passed on to gut bacteria. The likelihood of this process is not known but is considered to be low. When food is processed and also during digestion, components of bacterial cells are destroyed. Heat treatment will, however, not result in complete degradation of nucleic acids. While infectivity of a pathogen may be lost, intact or fragmented nucleic acid may persist. In principle, such fragments might be taken up by bacteria in the gut and become integrated into their genetic material. Whether the length of such fragments is sufficient to transfer characteristics such as antibiotic resistance is unknown. However, the transfer of resistance via this pathway is at present considered highly unlikely.

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[21] Zero-tolerance is applied by some countries, for example, to *Listeria monocytogenes* in ready-to-eat food. It was also used in relation to *E. coli* O157:H7 and *Salmonella*. As the detection limit of microbiological tests keeps improving, the definition of "zero" remains a moving target.

If live bacteria are ingested, the extent to which these are able to establish themselves in the human gut is uncertain. Some bacteria are able to resist digestion and to colonize the human (or animal) gut. Knowledge on this critical step is patchy and sometimes contradictory[22]. Some researchers hypothesize that commensal bacteria in humans belong to different "pools" and that bacteria from food animals have limited ability to establish themselves in alternative hosts, including humans. If pathogenic bacteria survive digestion, this sometimes results in disease, most frequently in diarrhea. Among the most relevant bacteria causing diarrhea in the developed world are *Salmonella* and *Campylobacter*. If antibiotic treatment is not required, the fact that the organism is resistant should not have any clinical consequences for the patient. This is the true for most human cases. Some reports indicate, however, that resistant bacteria could cause more severe disease.

Additionally, live bacteria in food provide resistance genes that can be passed on to bacteria of the normal flora that is always present in the gut. Transfer is particularly common for genes located on mobile genetic elements; such transfer is widely documented for a range of genes and pathogens[23]. However, evidence is so far mostly based on laboratory studies and only confirmed in a few animal experiments for specific scenarios. Such gene transfer can be facilitated by bacteriophages.

Generally, the causative link between occurrence of resistant bacteria in food and in consumers is challenging to prove and has only been fully established for a few examples. The availability of laboratory technologies[24] that allow for easy comparison of the genome between individual bacteria isolates as well as entire bacterial populations provides novel opportunities to investigate the risk of resistance transfer via food. Using such methods, it was possible to show that resistance transfer can also occur from humans to animals. It was documented that resistance genes can be acquired and lost

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[22] Lazarus, B., Paterson, D. L., Mollinger, J. L., et al. (2015). Do Human Extraintestinal Escherichia coli Infections Resistant to Expanded-Spectrum Cephalosporins Originate From Food-Producing Animals? A Systematic Review. *Clinical Infectious Diseases*, *60*(3), 439–452. doi:10.1093/cid/ciu785

[23] Poirel, L., Cattoir, V., & Nordmann, P. (2012). Plasmid-Mediated Quinolone Resistance; Interactions between Human, Animal, and Environmental Ecologies. *Frontiers in Microbiology*, *3*, 1–7. doi:10.3389/fmicb.2012.00024

[24] Next Generation Sequencing, often abbreviated as NGS

and acquired again repeatedly over time. By using such methods, it will be possible to investigate the risk of resistance emergence and transfer in a more quantitative way. This, however, also requires a more systematic approach to sampling and isolation of bacteria subject to such analysis to allow for a valid interpretation and reflection of the frequency of resistance occurrence and transfer and thus of the epidemiology of resistance at population level.

7. What can we do about it?

Although we do not fully understand the link between antimicrobial usage in farming and the occurrence of antibiotic resistant bacteria in food, some associations were demonstrated where data are available[25]. Regulation and restriction of antibiotic usage in animals is therefore an option to manage risk for consumers. In many countries it is the legal responsibility of the primary producer (i.e. the farmer) to assure the safety of food that is put on the market for consumers. However, in the absence of legal obligations, the motivation to reduce usage remains limited. Some countries have established reduction targets in an attempt to reduce the usage if antimicrobials in animal production[26]. Although these targets were established as a result of a political process rather than on the basis of scientific risk assessments, they created a momentum within the livestock sector that was previously not observed. Voluntary reduction efforts can also be successful. The only country that has had measures in place for some time is Denmark. However, it could be useful also to have a look to potential unintended consequences for such reduction focused restrictions. In Denmark large quantities of zinc oxide (ZnO) are used in swine. There are publications available linking the use of tetracyclines in combination with

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[25] Dutil, L., Irwin, R., Finley, R., et al. (2010). Ceftiofur resistance in Salmonella enterica serovar Heidelberg from chicken meat and humans, Canada. *Emerging Infectious Diseases*, *16*(1), 48–54. doi:10.3201/eid1601.090729

[26] Speksnijder, D. C., Mevius, D. J., Bruschke, C. J. M., & Wagenaar, J. A. (2015). Reduction of veterinary antimicrobial use in the Netherlands. The dutch success model. *Zoonoses and Public Health*, *62 Suppl 1*, 79–87. doi:10.1111/zph.12167

ZnO to a selection of MRSA in swine[27,28]. The fact is that Denmark experiences a very high prevalence of MRSA in swine, which has led to some export problems of swine meat. Environmental aspects of the use of ZnO are so far not completely investigated. The cornerstones of their continuing reduction of usage are the quantification of use in combination with compulsory specialist advice. This so-called “yellow card system” continues to be successful in reducing usage[29]. Other countries have also demonstrated a strong effect of reduction targets which indicates substantial room for a more targeted use of veterinary antibiotics.

Corporate initiatives by food processors to source only animals that were raised without the use of antibiotics are also reported. However, this approach raises welfare and ethical issues as it is not clear how farmers should deal with animals that become sick. It appears ethically unacceptable to destroy animals only because they require treatment. Also, even after complete removal of exposure to antimicrobials, the reduction of resistance among bacteria may not be instantaneous but protracted over time. Nevertheless, antibiotic-free production was adopted by some producer cooperatives (e.g. in France). New Zealand was the first country to announce the mid-term aspirational objective that usage of antimicrobials in food animals should be no longer required by 2030. This announcement is meant to unleash innovation including the breeding of high-health animals, early warning systems for accelerating and focusing farm management responses as well as replacement of treatment by innovative alternative therapy forms.

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[27] Moodley, Arshnee, Søren Saxmose Nielsen, and Luca Guardabassi. "Effects of tetracycline and zinc on selection of methicillin-resistant Staphylococcus aureus (MRSA) sequence type 398 in pigs." Veterinary microbiology 152.3 (2011): 420-423.

[28] Slifierz, M. J., R. Friendship, and J. S. Weese. "Zinc Oxide Therapy Increases Prevalence and Persistence of Methicillin-Resistant Staphylococcus aureus in Pigs: A Randomized Controlled Trial." Zoonoses and public health 62.4 (2015): 301-308.

[29] Jensen, H. H., & Hayes, D. J. (2014). Impact of Denmark’s ban on antimicrobials for growth promotion. *Current Opinion in Microbiology*, *19*, 30–6. doi:10.1016/j.mib.2014.05.020

As a general measure to reduce and focus antimicrobial usage, so-called prudent use guidelines were published by numerous organizations, mainly under the lead of the veterinary profession[30]. Prudent use should maximise therapeutic effect while minimising the development of resistance. While the exact content and wording of the guidelines varies, the recurring themes include the recognition of the responsibility of various partners involved in livestock production ranging from farmers to government authorities, prescription of antimicrobials by a veterinary professional, the need for laboratory-based diagnosis and sensitivity testing before treatment, as well as the selection of the appropriate substance and the use of licensed products.

In order to prevent undesired consequences of antimicrobials, it is best to prevent usage in the first place. In other words, to apply measures to generally increase health in food animals. This strategy is also supported by some governments, for example by the European Commission's strategy "prevention is better than cure". There is a substantial body of work regarding risk factors for infectious diseases in different farm animal species. Optimizing management practices to reduce the risk of disease is therefore indirectly reducing the need for treatments. It has been shown in a number of studies, that this approach can be effective. Measures including the prevention of disease introduction and spread (i.e. increased biosecurity), improving the quality of feed and water, optimizing animal housing systems and general improvement of hygiene can all be effective in an indirect way. These measures reduce the risk of disease and therefore the need for treatment with antibiotics. A recent study in four European countries showed that the introduction of measures on pig farms that were tailored to the preference of the farm managers resulted in a significant reduction of antimicrobial usage after only one year[31]. The same study also showed that the selection of measures should be taking into accounts the perceived needs and beliefs of farmers and veterinarians[32, 33].

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[30] Mateus, A., Brodbelt, D. & Stärk, K. (2011). Evidence-based use of antimicrobials in veterinary practice. *In Practice*, *33*(5), 194–202. doi:10.1136/inp.d2873
[31] Postma, M., Stärk, K. D. C., Sjölund, M., et al. (2015). Alternatives to the use of antimicrobial agents in pig production: A multi-country expert-ranking of perceived effectiveness, feasibility and return on investment. *Preventive Veterinary Medicine*, *118*(4), 457–66. doi:10.1016/j.prevetmed.2015.01.010
[32] Visschers, V. H. M., Backhans, A., Collineau, L, et al. (2015). Perceptions of antimicrobial usage, antimicrobial resistance and policy measures to reduce antimicrobial usage in convenient samples of Belgian,

The relationship between farmers and veterinarians is seen to be critical not only for successful management of health on the farm (and therefore reducing antimicrobial usage) but also to disseminate information on risks and benefits of antimicrobials and to generally inform farmers on options available to manage infectious diseases. Some online tools (see http://www.biocheck.ugent.be and http://www.abcheck.ugent.be) have already become available that help farmers assess their levels of biosecurity and the extent of antimicrobial usage on their farms. These tools can also be used for benchmarking and training. However, they are currently not available for all livestock species.

Vaccination could be a promising measure for disease prevention. However, vaccination campaigns may be costly and require diagnosis of the main pathogen causing disease. More evidence to quantify the costs and benefits of farm-level intervention options is expected from major research projects that are currently ongoing. These projects aim at assessing both the feasibility and the economic impact of prevention and control measures (follow, for example, http://www.effort-against-amr.eu/).

8. *Where are the (most important) knowledge gaps?*

Measures taken against antimicrobial resistance should be evidence-based. However, many pieces of the puzzle describing the complex relationships and dynamics in the resistance system remain unknown[34, 35]. This has been recognized and acknowledged repeatedly over recent years triggering a number of substantial research programs, the results of which are expected over the coming years. The following list of perceived knowledge gaps is therefore bound to be outdated very soon. Current

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French, German, Swedish and Swiss pig farmers. *Preventive Veterinary Medicine*. doi:10.1016/j.prevetmed.2015.01.018

[33] Visschers, V. H. M., Backhans, A., Collineau, L., et al. (2016). A Comparison of Pig Farmers’ and Veterinarians' Perceptions and Intentions to Reduce Antimicrobial Usage in Six European Countries. *Zoonoses and Public Health*. doi:10.1111/zph.12260

[34] Michael, C. A., Dominey-Howes, D., & Labbate, M. (2014). The antimicrobial resistance crisis: causes, consequences, and management. *Frontiers in Public Health*, *2*, 145. doi:10.3389/fpubh.2014.00145

[35] Landers, T. F., Cohen, B., Wittum, T. E., & Larson, E. L. (2012). A review of antibiotic use in food animals: perspective, policy, and potential. *Public Health Reports*, *127*(1), 4–22.

knowledge gaps relevant to the risk of antimicrobial resistance spread via animal-derived foods relate to three main areas:

1) How much antibiotic resistance does occur, how does it spread and how does it affect public health?
2) Which factors, other than "overuse" [36] of antibiotics, are influential in antibiotic resistance occurrence and therefore relevant for control?
3) What are the costs and benefits of control measures?

Regarding the first point, efforts are ongoing regarding standardized recording and monitoring of both resistance and usage, but it will take many years yet to close this gap. Massive differences remain between farms of similar size within the same country as to the volume of antimicrobials used, which can vary up to 10-fold. Projects attempting to quantify the link between usage in livestock and resistance in bacteria have also commenced, at least for specific scenarios. In general, we are largely ignorant of how resistance genes move within complex food systems and the implications of such dynamics for both animal and public health. The same is true regarding risk factors for resistance, both in relation to husbandry and animal health as well as farmer and veterinary behavior. Both microbiological and behavior studies are essential to provide a basis for evidence-based interventions. However, given the almost unlimited number of substance-bacteria-food combinations, there is a need for prioritization. Recent reviews show that despite the substantial number of studies already published, the resulting evidence remains highly fragmented and insufficient to address specific questions. This situation could be improved by combining risk assessment and other mechanisms for setting priorities with subsequent laboratory- and field-based studies. Qualitative research methods elucidating the reasoning and behavior of relevant decision-makers have not yet been fully exploited, leaving many gaps in areas that will be important if we are to achieve successful control. For example, an intervention that is effective in principle will be of limited value if the uptake by farmers in practice

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[36] http://www.cdc.gov/drugresistance/about.html

is low. Also, any intervention on a farm will come at a cost, so to know the benefits will be essential. If the beneficiaries are mainly outside the farming sector, funding mechanisms will have to be considered and possibly adjusted to provide the right incentives.

Major gaps remain in this context, such as estimates of the public health burden of antibiotic resistance in bacteria transferred via food. While some estimates are available for the costs of antibiotic resistance in hospital settings, it is not known to what extent exposure to resistant bacteria (or their genes) in food results in additional human cases and related costs for treatment, hospitalization and absence from work. In order to justify interventions in animal farming, the benefits for public health should be quantified. Such benefits clearly exist in terms of increased productivity as well as to assure animal welfare when animals get sick.

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