REDUCE ANTIBIOTICS - AVOIDING RESERVE ANTIBIOTICS IN FARM ANIMALS

Comparison of strategies in different European countries

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1. Antimicrobial resistance (AMR) is considered one of the greatest threats to human health worldwide. The World Bank compares the potential economic damage to the financial crisis of 2008. Without realising it, every human being can be colonised with bacteria that are resistant to antibiotics, i.e. no longer sensitive to them, fall ill from them and also transmit these bacteria to other people.

2. In animal production, animal welfare is considerably endangered by resistant bacteria if bacterial infections are no longer treatable. This not only affects the profitability of animal husbandry, but especially the biosecurity of animal products and the environment, and also human health due to the risk of transmission of resistance.

3. The high use of antibiotics in livestock farming contributes to the emergence of AMR. There is sufficient evidence to confirm the transmission of resistant bacteria between animals, humans and the environment.

4. In the past, disincentives have promoted the use of newer and very effective antibiotic groups (e.g. fluoroquinolones, 3rd and 4th generation cephalosporins) in humans and animals.

5. On the one hand, this was particularly due to the effectiveness of these agents in combating diseases, which was due to the fact that resistance was not yet so widespread. On the other hand, no sufficiently effective restrictions were imposed on users to the effect that these agents are demonstrably only to be used on pathogens for which no other antibiotics are effective (last-line/reserve antibiotics).

6. There are considerable differences in the EU with regard to the quantities of antibiotics used in animals. Thus, not only are there different routines of use, but the effectiveness of measures to reduce the consumption of antibiotics varies greatly between countries.

7. A harmonisation of measures along the lines of the countries with the lowest consumption is recommended. A digital collection and evaluation of data on the use of antibiotics in livestock farms should be carried out in all member countries and should be extended to other animal groups and species in the medium term. In addition to the recording of antibiotic quantities, the actual consumption should be determined as a comparable parameter.

8. The prescription of antibiotics must not be linked to an economic profit for veterinarians. The veterinary right not only to use or prescribe antibiotics but also to sell them at a profit should be prohibited in the member states, following the example of Denmark. At the same time, benchmarking can encourage both farmers and veterinarians to save on antibiotics.

9. Good animal health can also be achieved with reduced use of antibiotics. The example of Denmark makes it clear that low infection rates are possible even in intensive animal husbandry systems.

10. Disease prevention measures such as species-appropriate animal husbandry, lower stocking densities, performance-based feeding and water supply, effective external and internal biosecurity on the farm, and the use of vaccinations, probiotics and herbal substances are the basis for lower infection risks.

11. If antibiotics are used, they must be applied according to the known standards of rational antibiotic use. These include:

    - No prophylactic antibiotic administration
    - Use of antibiotics only on the basis of a disease diagnosis by a veterinarian and only for approved indications in appropriate dosages
    - Antibiotics for group treatments as part of metaphylaxis only in combination with other measures
    - Gradually phase out within 10 years the use of critically important human priority antimicrobials (HPCIA) in animals and comply with the OIE list of antimicrobials of veterinary importance

12. Alternatives in the prevention of antimicrobial resistance as well as rapid tests should be further scientifically investigated and promoted.

13. Research into new therapeutic approaches shall be encouraged. Herbal and other medicinal products which have proven themselves in human medicine as an alternative to antibiotics are to be authorised in veterinary medicine in a simplified procedure.

2. INTRODUCTION

Modern human and veterinary medicine are impossible to imagine without antibiotics. They enable the life-saving treatment of bacterial infections that were still fatal 80 years ago, such as pneumonia or blood poisoning. In surgical interventions, they serve to prevent infections and they protect people with a weakened immune system, e.g. during chemotherapy in the treatment of cancer.

In recent decades, life expectancy has improved significantly in both humans and pets in the EU. This is due to the quality of treatments, but also to the production of cheaper antibiotics and easy access to them, not only in high-income countries.

At the same time, the effectiveness of these drugs is decreasing worldwide because bacteria are becoming increasingly insensitive to antibiotics, i.e. resistant. All bacteria have the evolutionary ability to form resistances and can also pass this ability on to other bacteria that were previously sensitive to antibiotics.

Bacteria that are insensitive to antibiotics pose an immense threat because they can hardly be treated as pathogens. Antimicrobial resistance (AMR) is the greatest threat to human health worldwide. Multi-resistant microorganisms, i.e. microorganisms that are insensitive to several antibiotics, are spreading more and more. Since both humans and animals are affected by this and the resistant ones can be exchanged between humans, animals and the environment, one speaks of a "One Health Problem", an enormous threat to humanity.

The former non-therapeutic use of antimicrobials as performance enhancers in animal feed has significantly promoted the development of resistance. This has justifiably led to a ban on antibiotic performance enhancers in the EU. The amounts of antibiotics consumed to control disease vary widely in food-producing animals in the EU. As a result, the potential contamination of food also varies.

Milk has so far not posed a major risk as a carrier of antibiotic-resistant microorganisms to consumers because bacteria are killed by the pasteurisation of milk. This will change if the trend towards consumption of raw milk and its products continues to increase.[1]

Today, large quantities of antibiotics are used therapeutically and metaphylactically in young animals. These are mainly piglets, poultry and calves kept for fattening. Metaphylactic describes the situation where individual animals in a group of animals are ill, but the entire group is treated. Resistant bacteria are also transmitted to humans via direct contact with farm animals, the environment and also meat products.

1 WEBER, M. K. AND LIPSKI, A. (2017): Reducing the spread of antibiotic resistance through targeted hygiene measures. Faculty of Agriculture, University of Bonn, Schriftenreihe des Lehr- und Forschungsschwerpunktes USL, No. 188, 71

Young animals (e.g. piglets, broilers, turkeys, young chickens and calves) with a developing specific immune system are particularly susceptible to disease, so the use of antibiotics is highest in these groups of animals.

Group treatments are therefore suspected of compensating for the susceptibility of farm animals to disease due to poor hygienic conditions, inadequate housing conditions and inappropriate feeding.

The question arises whether this current practice, i.e. the routine "metaphylactic" use of antibiotics, is necessary and what possibilities exist for reducing it.

The aim of this study is therefore to examine the strategies of EU countries with high and low consumption of antibiotics in livestock farming. The aim is to find out which paths towards more animal health have been particularly successful so far, in order to be able to derive further political demands from this.

Bacterial resistance in animals is most effectively reduced by taking measures for better animal health and thus using fewer antibiotics. The goal is to significantly reduce metaphylactic use, i.e. the routine use of antibiotics. The EU has recognised this problem and implemented various laws to reduce antibiotic use in animals. However, success in reducing antibiotics varies widely across EU countries.

3. BASICS

3.1. ANTIBIOTIC RESISTANCE

3.1.1. ANTIBIOTICS

The word "antibiotic" is derived from the Greek, where "anti" means "against" and "bioticos" means "relating to life", and was originally introduced by Selman Waksman in 1947.[2]

Today, the term "antibiotic" defines natural, semi-synthetic or synthetic substances with antimicrobial activity. They are substances that have a bacteriostatic (i.e. growth-inhibiting) or bactericidal (bacteria-killing) effect. They influence various mechanisms that are crucial for bacterial cell function, e.g. the structure of the cell wall, cell growth, division or metabolic pathways of the bacteria. As chemotherapeutic agents, antibiotics are used in medicine to treat infections caused by various types of: Bacteria, fungi or protozoa. Some can also be used as anti-cancer drugs or immunosuppressants.[3]

3.1.2. RESISTANCES

Resistance is a natural response of bacteria to chemical threats from the environment that has evolved over millions of years of evolution.

Thus, multi-resistance to several antibiotics has been identified in bacteria that have existed for millions of years.[4] Nevertheless, resistance was much less detectable before the introduction of antibiotics in medicine.[5] Resistance can occur in most types of microorganisms, this includes not only bacteria but also fungi, parasites and viruses. A current database lists the existence of more than 20,000 potential resistance genes (R-genes) in almost 400 different types of bacteria, inferred from available bacterial genome sequences.[6]

Drug resistance occurs when bacteria develop efficient mechanisms to prevent drugs from working and thus become insensitive to them.

There is so-called primary resistance, which means that an antibiotic is fundamentally ineffective against a bacterium (e.g. cephalosporins for enterococci).

Secondary resistance usually arises from random mutations in the bacterial genome or on extrachromosomal DNA on plasmids, transposomes or integrons, which can also be passed on to other bacteria,

2 Waksman S.A. (1947). What is an antibiotic or an antibiotic substance? Mycologia, 39: 565-569
3 Davies J., Davies D. (2010). Origins and evolution of antibiotic resistance. Microbiol. mol. Biol. Rev, 74: 417-433 https://doi.org/10.1128/MMBR.00016-10
4 Bhullar K, Waglechner N, Pawlowski A, Koteva K, Banks ED, et al. (2012) Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome. PLOS ONE 7(4): e34953. https://doi.org/10.1371/journal.pone.0034953
5 Hughes VM, Datta N (1983) Conjugative plasmids in bacteria of the 'pre-antibiotic' era. Nature 302: 725-726.
6 Liu, B., and M. Pop. 2009. ARDB-Antibiotic Resistance Genes Database. Nucleic Acids Res. 37:D443-D447

- by horizontal gene transfer, if a microorganism contains corresponding genes
  - by conjugation, if the gene transfer takes place via direct contact between bacteria
  - by transduction (gene transfer via bacteriophages)
  - by transformation, which is the uptake of naked DNA from the environment and its incorporation into bacterial DNA (Holmes et al., 2016)
- via vertical transfer, i.e. when genes are passed down through generations.[7]

When microorganisms are exposed to an antibiotic over a longer period of time, an ecological niche is created, i.e. those germs are given a selection advantage that carry resistance genes against the active substance and/or form biofilms more quickly. Thus, any use of antibiotics in humans and animals can lead to the development of characteristics in bacteria that make them resistant to antibiotics.[8]

Biofilms are communities of bacteria, viruses and fungi in a protective shell produced by the pathogens themselves, which shields them from attack. Inside biofilms, the mutation frequency is stimulated and thus the chance of forming resistances. In addition, the cell wall permeability of bacteria in the biofilm is reduced.

Biofilms are now considered to be at least as important in the development of resistance to antibiotics as genetically fixed resistance. Thus, 90 percent of all bacteria have the ability to form biofilms and thus protect themselves from access by antibiotics and the immune system.[9]

Treatment with antibiotics often only kills bacteria in the outer areas of the biofilms, while the bacteria survive inside. There is evidence that the presence of antibiotics contributes directly to the formation of biofilms.[10]

The result is the survival of bacteria on the mucosal surfaces and thus a slow or chronic infection, regardless of whether these bacteria also contain resistance genes.[11]

3.1.3. TRANSMISSION CHANNELS

Bacteria with resistance properties can be transmitted between humans, between animals, and between humans, animals and the environment. The transmission and spread of bacteria or genes carrying resistance information can occur in hospitals, in the general population or through the food chain.[12]

7 Davies J., Davies D. (2010). Origins and evolution of antibiotic resistance. Microbiol. mol. Biol. Rev, 74: 417-433 https://doi.org/10.1128/MMBR.00016-10

8 ibid

9 Luanne Hall-Stoodley; Paul Stoodley (2009). Evolving concepts in biofilm infections. Cellular Microbiology (2009)11(7),1034–1043. https://Doi.org/10.1111/j.1462-5822.2009.01323.x

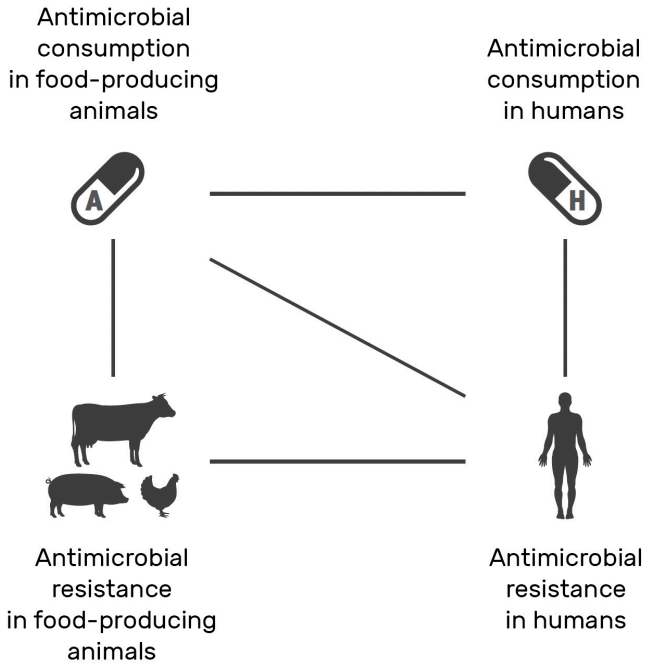
10 Oliveira NM, Martinez-Garcia E, Xavier J, Durham WM, Kolter R, et al. (2015) Correction: Biofilm Formation As a Response to Ecological Competition. PLOS Biology 13(8): e1002232. https://doi.org/10.1371/journal.pbio.1002232

11 Yang L, Liu Y, Wu H, Høiby N, Molin S, Song Z. Current understanding of multi-species biofilms. Int J Oral Sci 2011: 3: 74-81. https://doi.org/10.4248/IJOS11027

12 European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA). Third joint inter-agency report on integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA. EFSA Journal 2021;19(6):6712 https://doi.org/10.2903/j.efsa.2021.6712

There are differences in the main transmission routes of pathogenic bacteria, so that a differentiated assessment becomes necessary.[13]

[14]



In livestock farms, transmission occurs from animals to humans and vice versa, from animal to animal, as well as via animal food or through plant products fertilised with animal manure. Resistant germs can also enter groundwater and thus the food cycle via manure.[15] Avoiding the use of antibiotics in animals and thus reducing the pressure on bacteria to develop resistance thus seems to be the most effective approach.[16]

3.2. DEFINITIONS

The Veterinary Medicinal Products Regulation 2019/6 EU distinguishes between different areas of application for antibiotics. In addition to the therapy of sick animals, the terms prophylaxis and metaphylaxis are important, as the largest amounts of antibiotics are consumed in animals via these routes.

13 ibid
14 ibid
15 https://www.bag.admin.ch/bag/de/home/strategie-und-politik/nationale-gesundheitsstrategien/strategie-antibiotikaresistenzen-schweiz.html
16 The authors

3.2.1. PROPHYLAXIS

Regulation 2019/6 EU defines "prophylaxis" as "the administration of a medicinal product to an animal or group of animals before clinical signs of disease appear in order to prevent disease or infection."[17]

Prophylaxis is also understood to mean the prevention of diseases through measures aimed at improving the health status of an animal or group of animals. This includes hygienic and feeding-related measures as well as vaccinations, husbandry management or influences of animal breeding.

Antibiotics should only be used in exceptional cases as a means of prophylaxis, for example in connection with previous operations or in treatments with suppressive effects on the immune system.

3.2.2. METAPHYLAXIS

Metaphylaxis, according to Regulation 2019/6 EU, is "the administration of a medicinal product to a group of animals following a diagnosis of clinical disease in part of the group, with the aim of treating the clinically ill animals and containing the spread of disease to those animals in close contact and at risk, and which may already be subclinically infected."[18]

In the case of metaphylactic treatments, it is thus not defined how many animals of a herd or epidemiological unit must be ill in order to justify the use of antibiotics. The question of proof of the disease is also not clarified.

As this enables regular, routine use, e.g. in fattening herds, criteria and restrictions for metaphylactic use of antibiotics would be necessary.

3.3. IMPORTANCE OF ANTIBIOTIC RESISTANCE FOR HUMANS

In Europe, about 670 000 people become infected with antibiotic-resistant bacteria every year. Rising antibiotic resistance is one of the biggest challenges in the health system both globally and in the EU. These bacteria, which are insensitive to antibiotics, are responsible for about 33,000 deaths per year in the EU.[19] These deaths are preventable if effective measures are taken to reduce antibiotic use in both human and veterinary medicine.

17 REGULATION (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32019R0006&from=DE

18 ibid

19 Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019;19(1):56–66. https://doi.org/10.1016/S1473-3099(18)3060

The cost of these pathogens to the health systems of EU/EEA countries is about €1.1 billion per year.[20]

The World Bank puts the losses relative to a world without antimicrobial resistance at $85 trillion in gross domestic product and $23 trillion in global trade between 2015 and 2050.[21]

Effective antibiotics are indispensable for modern medicine, especially in hospitals, but also in the outpatient sector, for example with family doctors. There is global agreement that antibiotic resistance poses an increasing threat to public health and the healthcare system. However, the effectiveness of antibiotics is declining due to increasing antibiotic consumption and the resulting selection pressure for resistance among bacteria. At the same time, more than one million children die each year worldwide from untreated pneumonia and sepsis because they do not have access to antibiotics.[22]

Rising incomes, more health insurance and a high burden of infectious diseases are increasing antibiotic consumption and, as a result, antibiotic resistance in bacteria worldwide.

Between 2000 and 2010, antibiotic consumption increased by 36% in 71 countries. The countries Brazil, Russia, India, China and South Africa (BRICS) in particular are responsible for three quarters of these increases.[23] [24]

High antibiotic consumption rates (in humans) from 2000-2018 occurred in high- and middle-income countries in North America, Europe and the Middle East, contrasting with very low consumption rates in sub-Saharan Africa and parts of Southeast Asia. The highest antibiotic consumption exists in high average income countries, with countries such as the USA classifying up to 30% of antibiotic prescriptions as unnecessary. The lowest antibiotic consumption rates are in sub-Saharan Africa, a region characterized by the highest prevalence of sepsis. Thus, consumption primarily reflects the financial situation of the countries and the availability of funds rather than the real need.[25]

The threat of infections with resistant bacteria in the EU is comparable to the burden of influenza, tuberculosis and HIV/AIDS combined. Almost 40% of infections with resistant bacteria are caused by pathogens resistant to last-line / reserve antibiotics such as carbapenems and colistin. This is a significant increase compared to 2007.[26]

Antibiotics which, **from a therapeutic and microbiological point of view,** should preferably be used for the treatment of a bacterial infection, depending on the respective pathogen, are

20 ECDC; OECD.Antimicrobial Resistance-Tackling the Burden in the European Union-Briefing Note for EU/EEA Countries; OECD:Paris, France, 2019.

21 Ahmed et al.: Assessing the Global Economic and Poverty Effects of Antimicrobial Resistance. World Bank Group 2017. https://documents1.worldbank.org/curated/en/190151498872848485/pdf/WPS8133.pdf

22 Laxminarayan, R.; Matsoso, P.; Pant, S.; Brower, C.; Røttingen, J.-A.; Klugman, K.; Davies, S. Access to effective antimicrobials: A worldwide challenge. Lancet 2016,387, 168-175. https://doi.org/10.1016/S0140-6736(15)00474-2

23 Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 2014; 14: 742-50 https://doi.org/10.1016/S1473-3099(14)70780-7

24 Klein et al: Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000-15: an analysis of pharmaceutical sales data. Lancet Infect Dis 2021; 21, 1, 107-115, https://doi.org/10.1016/S1473-3099(20)30332-7

25 Browne et al. Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. Lancet Planet Health 2021; 5: e893-904. https://doi.org/10.1016/S2542-5196(21)00280-1

26 WHO Regional Office for Europe/European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022 - 2020 data. Copenhagen: WHO Regional Office for Europe; 2022. https://apps.who.int/iris/bitstream/handle/10665/351141/9789289056687-eng.pdf?sequence=1&isAllowed=y

called first-line antibiotics (1st line). Second-line antibiotics (2nd line) should only be used if these preparations are ineffective or contraindicated. Only if there is no demonstrable success with these drugs is treatment with third-line or last-line antibiotics recommended. These often include preparations that are classified as reserve antibiotics. However, due to their good efficacy, second- or third-line preparations are often used as the first choice, contrary to the recommendations.

It is therefore estimated that antibiotic resistance (AMR) to second-line antibiotics will increase by 72% in 2030 in the EU/European Economic Area (EEA) compared to 2005. Over the same period, AMR in last-line antibiotics will more than double unless effective action is taken.[27]

3.4. RESERVE ANTIBIOTICS IN ANIMALS

The use of antibiotics in food-producing animals has increasingly become the focus of public interest in recent years.

The WHO defines the criteria for classifying antibiotics as "Critically important antimicrobials (CIA)" if they are used to treat

- As the only or one of the few available therapies for the treatment of severe bacterial infections in humans.

are used and when they are

- Caused by bacteria that can be transmitted to humans from other non-human (animal sources), or
- Caused by pathogens that can acquire resistance genes from non-human sources

If the following points are also fulfilled, the antibiotic groups are classified as (Highest Priority Critically Important Antimicrobials for Human Medicine, HPCIA)

- Used to treat large numbers of people with infections for which there are limited antimicrobials available
- Often used in human medicine or for certain high-risk groups
- Used to treat infections in humans for which there is extensive evidence of transmission of resistant bacteria or genes from non-human sources[28]

Reserve antibiotics with the highest priority for human medicine (Highest Priority Critically Important Antimicrobials for Human Medicine, HPCIA), which are also approved for animals, comprise five classes of active substances: Polypeptides (colistin), fluoroquinolones, 3rd and

27 ECDC; OECD.Antimicrobial Resistance-Tackling the Burden in the European Union-Briefing Note for EU/EEA Countries; OECD:Paris, France, 2019.

28 WHO Critically important antimicrobials for human medicine, 6 th revision, Geneva 2019 ISBN 978-92-4-151552-8 https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf

4th generation cephalosporins and macrolides.[29] Colistin is mainly used orally in calves, poultry and pigs, while 3rd + 4th generation cepahalosporins are approved as injection preparations and mastitis preparations. The fluoroquinolones are used orally and as injectables in pigs and cattle frequently for diarrhea and respiratory infections. The macrolides are used as injectables and orally mainly for respiratory infections.

Using the example of poultry production with high stocking densities and also comparatively high antibiotic use, correlations between the use of the agents and increased resistance can be well demonstrated.

Resistance rates for fluoroquinolones and quinolones are significantly lower in the USA compared to other large poultry producing countries. The use of fluoroquinolones is not permitted in the USA. Raising broilers without fluoroquinolones can thus demonstrably lead to low resistance rates.[30]

There is evidence of an association between consumption of fluoroquinolones commonly used in poultry and resistance to fluoroquinolones in human E. coli in 2016-2018.[31]

In Spain, the AMR against ciprofloxacin for E.coli in poultry increased from 17% in 2001 to 91% in 2016, and that of nalidixic acid from 60% in 2001 to 88% in 2014.[32]

The primary goal of the WHO and the EU Commission is to prevent a further deterioration of the resistance situation and to achieve a reduction in the use of antibiotics, especially HPCIA, and here above all in veterinary medicine. This reduction can be achieved through the avoidance of infections and through appropriate hygiene measures, as well as in the field of veterinary medicine through improvements in breeding, husbandry, feeding and the well-founded expertise of animal keepers.

The measures taken so far by the EU and at national level have already led to a significant reduction in antibiotic consumption in animals. However, further efforts are needed to achieve further reductions, especially in HPCIA. In contrast, the consumption of antibiotics in humans remained at a constant level between 2014 and 2018, while a decrease was noticeable from 2019 onwards, which may be due to the Corona epidemic.[33]

29 WHO Critically important antimicrobials for human medicine, 6 th revision, Geneva 2019 ISBN 978-92-4-151552-8 https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf

30 Roth et al. The application of antibiotics in broiler production and the resulting antibiotic resistance in Escherichia coli: A global overview. 2019 Poultry Science 98:1791-1804 http://dx.doi.org/10.3382/ps/pey539

31 European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA). Third joint inter-agency report on integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA. EFSA Journal 2021;19(6):6712 https://doi.org/10.2903/j.efsa.2021.6712

32 Roth et al. The application of antibiotics in broiler production and the resulting antibiotic resistance in Escherichia coli: A global overview. 2019 Poultry Science 98:1791-1804 http://dx.doi.org/10.3382/ps/pey539

33 https://www.ecdc.europa.eu/en/publications-data/infographic-consumption-antibiotics-humans-and-food-producing-animals-eueea-2014

3.5. LEGAL CONTEXT

Under Regulation (EC) No 851/2004, the European Centre for Disease Prevention and Control (ECDC) is mandated to collect and analyse data and information on emerging public health threats and developments in order to protect public health in the EU.[34]

Furthermore, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project was launched by the European Medicines Agency (EMA) in September 2009, following a request from the European Commission to develop a harmonized approach to collecting and reporting data on antimicrobial consumption in animals.[35]

Data on bacterial resistance in humans are collected in two surveillance networks: the European Antimicrobial Resistance Surveillance Network (EARS-Net) and the Food- and Waterborne Diseases and Zoonoses Network (FWD-Net).

On 28 January 2022, the new Regulation (EU) 2019/6 of 11 December 2018 on veterinary medicinal products entered into force. The regulation includes provisions on the authorization and post-authorization measures, manufacture, import and export, dispensing, use of veterinary medicinal products as well as restrictions and sanctions. It replaces the previously applicable Veterinary Medicinal Products Directive (Directive 2001/82/EC). This regulation also further restricts the use of antimicrobial agents in animal husbandry in order to slow down the emergence and spread of resistance.[36]

Art. 37 (4) of the Regulation stipulates that the EU Commission can submit lists for this purpose by delegated act, with which individual antimicrobial active substances can be reserved solely for human medicine and thus be banned for use in veterinary medicine.

This act was implemented by Commission Implementing Regulation (EU) 2022/1255 of 19 July 2022.[37]

Accordingly, the listed substances to be reserved for the treatment of certain infections in humans must fulfil three criteria:

A Criterion of major importance for human health

> "it is (...) the only reserve antibiotic available (...) for serious life-threatening infections in humans that can lead to highly debilitating morbidity or high mortality if not treated appropriately".

34 Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European Centre for Disease Prevention and Control https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32004R0851&from=DE

35 Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2002R0178:20080325:de:PDF

36 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32019R0006&from=DE

37 Commission Implementing Regulation (EU) 2022/1255 of 19 July 2022 on the identification of antimicrobial active substances or groups of antimicrobial active substances to be reserved for the treatment of certain human infections in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council. https://eur-lex.europa.eu/legal-content/DE/TXT/HTML/?uri=CELEX:32022R1255

"it is an essential component (...) in a treatment concept (...) for severe life-threatening infections (...)".

"it is an antimicrobial active substance (...) (authorised) in the Union for the treatment of severe microbial infections in patients with limited treatment options (...) (with) a recognized unmet medical need related to antimicrobial resistance (...)".

B Risk of resistance transmission criterion

is fulfilled in the case of evidence of actual occurrence, spread and transmission of resistance to this active substance or cross-resistance, co-selection of resistance to other antimicrobial substances

is fulfilled in case of significant risk of transmission of such resistance from animal sources to humans

C Criterion of non-essential needs in the animal health sector

if "(...) there is no strong evidence that antimicrobial agents (...) are needed in veterinary medicine.

"the antimicrobial active substance (...) is used for the treatment of serious life-threatening infections in animals which, if not adequately treated, result in high morbidity or high mortality (...) but suitable alternative medicinal products are available for the treatment of these infections in the species concerned

"antimicrobial agents or groups of antimicrobial agents are used to treat serious life-threatening infections in animals (...) but there is scientific evidence demonstrating an overriding public health interest in not using them".[38]

The Commission's published list does not include any of the antibiotics defined by the WHO as HPCIA for humans and authorised in the EU for animals. This means that the opportunity to ban these antibiotics, which are so essential for human medicine, for animals was not taken.

38 Commission Delegated Regulation (EU) 2021/1760 of 26 May 2021 supplementing Regulation (EU) 2019/6 of the European Parliament and of the Council by laying down criteria for the designation of antimicrobial agents to be reserved for the treatment of certain human infections. https://eur-lex.europa.eu/legal-content/DE/TXT/HTML/?uri=CELEX:32021R1760&from=DE

4. USE OF ANTIBIOTICS IN FARM ANIMALS IN THE EU AND IN SELECTED COUNTRIES

4.1. ANTIBIOTICS IN FARM ANIMALS IN THE EU

The data basis for determining the quantities of antibiotics used are the annual sales by veterinary manufacturers of veterinary antibiotics for food-producing animals, including horses and fish from fish farms. ESVAC collects and publishes this data. The measure used is mg substance/PCU.[39]

The population correction unit (PCU) is a theoretical unit of measurement developed by the European Medicines Agency (EMA) in 2009 and introduced throughout Europe. It considers the animal population of a country over one year and the estimated weight of each species at the time of treatment with antibiotics.

For example, a value of 50 mg/PCU for food-producing animals would mean that, on average and over the course of a year, 50 mg of the antibiotic active ingredient per kg body weight was used at the time of treatment. To determine the PCU, adjustments are made to account for imports and exports of animals from and to other European countries.[40]

Sales data in the form of quantity data are relatively easy to obtain by the drug companies and are therefore frequently used. However, the data are mainly influenced by the dose of the substances.

In addition, sales do not necessarily correspond to use on animals, as losses, unused quantities, veterinary stockpiles and other factors may contribute to less being used on animals.

In contrast to the quantities sold, the number of daily doses used (nUDDvet) shows the actual number of treatments applied, which would be closer to the reality in the farms.

In addition, fluoroquinolones, third/fourth generation cephalosporins and macrolides, which pose a potential risk to human health, are used in low doses or as one-shot preparations. Their use thus contributes to a reduction in quantity, but not to a reduction in daily doses.

Now that EU-wide reporting of the antibiotics actually consumed and benchmarking in the animal sector has been implemented, the daily doses consumed should be recorded in addition to the consumption figures.

39 "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, pp. 51-52.

40 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/580710/1101060-v1-Understanding_the_PCU_-_gov_uk_guidance.pdf

Measuring antibiotic use should help to promote the sustainable use of antimicrobials to reduce the burden of resistant bacteria and thus improve animal health and welfare and consumer protection.[41]

Sales figures of antibiotics by country from 2010-2020 in mg substance/PCU

Country	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Highest and lowest value
Austria	62,9	54,4	54,8	57,2	56,3	50,7	46,1	46,7	50,2	42,6	46,3	62,9 42,6
Belgium	179,9	175,1	162,9	156,4	158,1	149,9	139,9	131,1	113,0	101,9	103,4	179,9 101,9
Bulgaria		92,6	98,9	116,1	82,9	121,8	155,2	129,8	119,6	112,7	166,00	166,0 82,9
Croatia					103,5	90,5	83,6	68,0	70,8	62,8	68,6	103,5 62,8
Cyprus		407,5	396,4	425,7	391,3	434,1	453,3	423,0	466,5	399,7	393,9	466,5 391,3
Czech Republic	94,3	83,0	79,8	82,2	79,8	68,0	61,2	63,5	57,0	53,8	56,3	94,3 53,8
Denmark	47,1	42,1	43,7	44,5	43,8	41,8	40,4	38,9	37,8	37,1	37,2	47,1 37,1
Estonia	76,8	70,5	62,7	70,1	76,8	64,9	63,7	56,3	52,9	53,5	49,2	76,8 49,2
Finland	22,0	21,3	21,3	21,8	21,8	19,9	18,1	18,9	18,2	19,1	16,2	22,0 16,2
France	133,6	114,3	101,1	93,9	105,8	69,4	71,2	68,0	64,2	58,3	56,6	133,6 56,6
Germany		211,5	204,8	179,7	149,3	98,2	89,2	89,1	88,4	78,6	83,8	211,5 78,6
Greece						57,4	63,6	94,2	91,2	83,2	89,1	94,2 57,4
Hungary	269,9	192,5	245,7	230,6	193,0	211,4	187,0	190,9	180,5	189,7	169,9	269,9 169,9
Iceland	6,8	6,0	5,4	4,9	4,8	4,7	4,5	4,4	4,8	3,5	3,8	6,8 3,5
Ireland	51,4	46,4	54,8	55,7	47,5	50,8	52,0	46,5	45,9	40,8	47,0	55,7 40,8
Italy	421,1	371,0	340,9	301,5	332,3	321,9	294,7	273,7	244,0	191,1	181,8	421,1 181,8
Latvia	39,4	36,7	41,5	37,6	36,6	37,6	29,9	33,2	35,9	41,1	30,8	41,5 29,9

41 Merle R, Meyer-Kühling B. Sales data as a measure of antibiotics usage: Concepts, examples and discussion of influencing factors. Vet Med Sci. 2020 Feb;6(1):154-163. https://doi.org/10.1002/vms3.205

Lithuania	48,2	41,1	39,1	29,0	35,5	35,0	37,4	34,2	32,7	20,8	20,5	48,2 20,5
Luxembourg			43,2	52,1	40,6	34,5	35,4	35,1	33,6	29,0	29,0	52,1 29,0
Malta								129,3	153,4	110,3	116,1	153,4 110,3
Netherlands	146,0	113,7	74,8	69,9	68,4	64,4	52,7	56,2	57,4	48,2	50,2	146,0 48,2
Norway	3,9	3,5	3,7	3,5	3,0	2,8	2,8	3,0	2,9	2,3	2,3	3,9 2,3
Poland		126,3	134,1	150,3	139,5	137,9	128,4	163,9	168,3	185,2	187,9	187,9 126,3
Portugal	178,0	161,8	157,2	187,2	201,7	170,3	208,0	134,2	186,6	146,6	175,8	208,0 134,2
Romania					109,0	100,5	85,2	90,1	82,7	53,9	57,8	109,0 53,9
Slovakia		43,6	43,3	59,2	65,6	50,8	50,3	61,8	49,2	42,3	51,9	65,6 42,3
Slovenia	46,8	46,0	36,9	22,3	33,3	26,3	30,3	36,6	43,2	44,9	33,3	46,8 22,3
Spain	259,5	335,8	302,3	317,0	418,8	402,0	362,4	230,2	219,0	126,7	154,3	418,8 126,7
Sweden	14,7	13,1	13,0	12,2	11,1	11,4	11,7	11,3	12,1	11,1	11,1	14,7 11,1
Switzerland					56,8	50,6	46,6	40,1	40,2	35,7	34,3	56,8 34,3
UK	67,8	51,0	66,2	62,5	62,3	56,5	39,0	32,1	29,0	30,5	30,1	67,8 29,0

Since the table only shows the total amount of antibiotics, it is of course interesting to check especially the consumption of the reserve antibiotics. Here, the fluoroquinolones, a group that can also be administered orally, follow as an example.

Sales of fluoroquinolones for food-producing animals in mg/PCU, by country, from 2010 to 2020[42]

Country	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Highest and lowest value
Austria	0,6	0,6	0,5	0,6	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,6 0,5
Belgium	0,7	0,8	0,9	1,0	1,1	1,0	0,6	0,2	0,2	0,2	0,3	1,1 0,5
Bulgaria		5,0	6,1	6,8	1,8	5,3	4,9	5,6	6,0	4,1	3,7	6,8 1,8
Croatia					3,4	3,1	2,5	1,8	2,2	2,0	2,1	3,4 1,8
Cyprus		0,5	0,8	0,9	0,9	1,1	1,6	2,4	3,1	2,2	2,2	3,1 0,5
Czech Republic	1,3	1,5	1,8	1,8	1,8	1,7	1,7	1,9	1,8	1,8	1,9	1,9 1,3
Denmark	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01 <0,01
Estonia	2,5	2,3	1,1	1,7	1,6	1,8	1,3	1,3	1,2	1,1	1,1	2,5 1,1
Finland	0,2	0,2	0,2	0,2	0,2	0,1	0,1	0,1	0,1	0,1	0,1	0,2 0,1
France	0,6	0,6	0,6	0,6	0,6	0,3	0,2	0,2	0,1	0,1	0,1	0,6 0,1
Germany		0,9	1,2	1,4	1,4	1,1	1,0	1,1	0,9	0,7	0,8	1,4 0,7
Greece						1,7	2,2	2,7	2,2	1,6	2,0	2,7 1,6
Hungary	8,8	6,7	11,0	9,2	9,1	9,5	9,6	8,8	10,8	12,2	11,6	12,2 6,7
Iceland	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01 <0,01
Ireland	0,4	0,4	0,6	0,5	0,4	0,4	0,5	0,4	0,4	0,3	0,4	0,6 0,3
Italy	1,7	2,2	2,5	2,3	3,1	2,9	2,3	3,0	2,3	1,8	1,2	3,0 1,2
Latvia	4,1	2,2	1,7	2,1	1,6	1,1	0,8	1,1	0,9	1,3	1,5	4,1 0,8
Lithuania	0,7	0,4	0,6	0,8	3,1	1,7	1,0	0,8	2,2	1,5	1,3	3,1 0,4
Luxembourg			0,7	0,8	0,7	0,7	0,8	0,7	0,8	0,8	0,8	0,8 0,7
Malta								15,2	4,6	8,4	4,4	15,2 4,4

42 "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, pages 59-60.

Netherlands	0,5	0,5	0,2	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,05	0,5 0,05
Norway	0,01	0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	<0,01	0,01 <0,01
Poland		7,1	8,2	8,8	9,0	8,5	9,7	11,0	10,9	13,2	12,9	7,1 13,2
Portugal	5,6	8,4	9,4	8,2	11,4	8,8	8,9	3,5	7,6	6,2	7,3	11,4 3,5
Romania					5,3	6,1	3,3	4,3	6,0	5,2	5,7	6,1 3,3
Slovakia		3,0	3,2	2,8	4,2	2,9	3,6	3,4	3,0	3,2	3,4	4,2 2,8
Slovenia	2,6	5,9	4,1	1,8	4,0	3,0	2,9	2,9	2,8	1,8	1,0	5,9 1,0
Spain	8,8	9,2	10,2	9,3	9,9	9,0	8,5	4,9	5,6	3,6	3,7	10,2 3,7
Sweden	0,1	0,1	0,1	0,04	0,03	0,02	0,02	0,02	0,03	0,02	0,02	0,1 0,02
Switzerland					0,5	0,5	0,3	0,3	0,2	0,2	0,2	0,5 0,2
UK	0,3	0,3	0,3	0,4	0,4	0,3	0,2	0,2	0,1	0,1	0,1	0,4 0,1

4.2. NON-RECORDED ACTIVE SUBSTANCES WITH ANTIBIOTIC EFFECT

In addition to the use of antibiotics approved as medicinal products, the poultry industry often adds routine coccidiostats, especially ionophoric antibiotics to feed.

Ionophores include monensin, lasalozide, salinomycin, narasin, maduramicin. These are polyether antibiotics that reversibly form chelates or other complexes with various inorganic cations. They have a lipophilic exterior, which is why they serve as ion carriers through otherwise impermeable biological membranes. This causes disturbances in the cation balance of living cells, such as coccidia.

In addition to their coccidiostatic effect, polyether antibiotics also have an antimicrobial effect against gram-positive bacteria and a partial antifungal effect against fungi/yeasts and antiviral effects against animal pathogenic (herpes) viruses.[43]

Some of these ionophores are also used today as so-called coccidiostats as feed additives and thus do not fall under the coverage as veterinary drugs. According to the FDA definition (USA), ionophores are antibiotics. This also means that ionophores can be used in the EU

43 Noack et al. 2019. Anticoccidial drugs of the livestock industry. Parasitology Research volume 118, 2009–2026. https://link.springer.com/article/10.1007/s00436-019-06343-5

without being covered by antibiotic monitoring and there are no statistics on how much of these substances are consumed in the EU.

The total use of ionophores is likely to be very high in many European countries. Published data from the UK can serve as an example. In 2013, 420 tonnes of antibiotics were sold, 355 tonnes of which were for all farm animals together. In terms of coccidiostats, 289 tonnes of active substance were sold, 209 tonnes of which were ionophores. This means that the amount of coccidiostats considerably exceeds the amount of antibiotics used for poultry.[44]

The use of ionophores was also reported in Finland and in 2020 the total amount was 20.8 tonnes, which also exceeds the 8.9 tonnes of medicated antibiotics used in all species.[45]

Ionophores are only approved for the suppression of coccidiosis in poultry. But they are also known to be used more frequently than non-antibiotic coccidiostats. Necrotic enteritis, caused by Clostridium perfringens, is one of the most important intestinal diseases in poultry and a high cost factor for intensive poultry farming. Some antibiotics are approved to prevent or treat the infection. In practice, the widespread use of ionophores replaces the use of other antibiotics, although ionophores are not licensed for this purpose.[46] [47]

In the UK, the British Poultry Council (BPC) represents about 90% of the poultry sector (chickens, turkeys, ducks and geese). Between 2012 and 2019, the BPC reduced total antibiotic use by 76% and critically important antibiotics by 97.3% to a total of 19.7 tonnes.[48] In contrast, the consumption of coccidistatics in 2019 is 280 tonnes.[49]

This very high level of routine medication with ionophores is due to the ongoing health problems of many intensive poultry farms. The figures suggest that ionophores may have been used to reduce the use of medicated antibiotics in the UK poultry industry without improving animal health or husbandry practices.

In addition, there has been evidence in Norway for some years that the use of narasin, an ionophore, in poultry can increase the number of enterococci bacteria in poultry that are resistant to the human antibiotic vancomycin through so-called co-selection.[50] Vancomycin-resistant enterococci (VRE) can cause severe infections in humans and can also be transmitted from animals to humans.[51] Therefore, Norway has banned the use of Narasin in the poultry industry since 2016.

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44 Borrellio, P. 2013 UK Veterinary Antibiotic Resistance and Sales Surveillance UK- VARSS 2013 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/440744/VARSS.pdf

45 https://www.ruokavirasto.fi/globalassets/viljelijat/elaintenpito/elainten-laakitseminen/antibioottiresistenssin_seuranta/finnish_food_authority_publications_6_2021_finres-vet_2020.pdf

46 https://www.msdvetmanual.com/poultry/necrotic-enteritis/overview-of-necrotic-enteritis-in-poultry

47 Lanckriet et al., 2010. The effect of commonly used anticoccidials and antibiotics in a subclinical necrotic enteritis model, Avian Pathology, https://hal.archives-ouvertes.fr/hal-00557321/document

48 https://britishpoultry.org.uk/bpc-antibiotics-report-2020

49 https://britishpoultry.org.uk/bpcs-response-to-bbc-countryfiles-coverage-on-the-use-of-ionophores-antiparasitics/

50 Report from the Norwegian Scientific Committee for Food Safety (VKM) 2015: 30 The risk of development of antimicrobial resistance with the use of coccidiostats in poultry diets, https://vkm.no/download/18.2994e95b15cc5450716152d3/1498142579152/0025301628.pdf

51 Simm et al. 2019, Significant reduction of vancomycin resistant E. faecium in the Norwegian broiler population coincided with measures taken by the broiler industry to reduce antimicrobial resistant bacteria, PloS One, https://doi.org/10.1371/journal.pone.0226101

4.3. ANTIBIOTICS IN THE IMPORT AND EXPORT OF ANIMALS

Transporting live animals is a considerable stress for the animals. The stress compromises the immune system. Due to the common transport of animals of different origins and the extremely close confinement on the transporters, bacteria are transferred from one animal to the next. This also applies to the resistance potential of the pathogens that are thus spread in Europe. To prevent infections caused by crowding, the animals are given antibiotics more frequently after transport. If this system of transports were reduced, a major reason for antibiotic administration in young animals would also be reduced.

From a legal point of view, it must be considered that imports of meat and animals from third countries are basically subject to the same conditions as transports within Europe. Thus, the prohibitions and restrictions regarding the use of medicines also apply.

In the following, the example of piglets is used to show how the trade flows take place.

4.3.1. SPECIAL PROBLEMS WITH PIGLETS

A wide variety of events and conditions can lead to animal health problems and thus to the potential use of antibiotics. In pig production, the transport of animals from the piglet producers to the final fatteners is problematic in many respects. When piglets are removed from the herd or reintroduced into the herd, groups of piglets with different origins and therefore different health risks are mixed together, which greatly increases the infection pressure on the animals. Injuries can also occur during the sometimes very long transport itself, which can become infected and may have to be treated with antibiotics. In addition, piglets at this age are generally more susceptible to bacterial contamination, as their specific immune system is still developing. Resistant bacteria may also be transported with the animals from one livestock farm to another and across national borders. The trade in live animals and their transport thus also contributes to the promotion of bacterial resistance.

4.3.2. INACCURACIES IN STATISTICAL RECORDING

Statistically, animal transports within the EU and also across its borders are recorded in two categories: live pigs weighing less and live pigs weighing more than 50 kilos. The former are mostly piglets weighing between 25 and 30 kilos that are transported to the final fattener, while the latter are finished pigs that are transported to the slaughterhouse. Finished pigs are transported across national borders much less frequently than piglets. However, weaned piglets may also be among the pigs transported. These are piglets weighing around eight kilos that are fattened for a few weeks in a specialised farm after weaning from the sow for intermediate fattening.

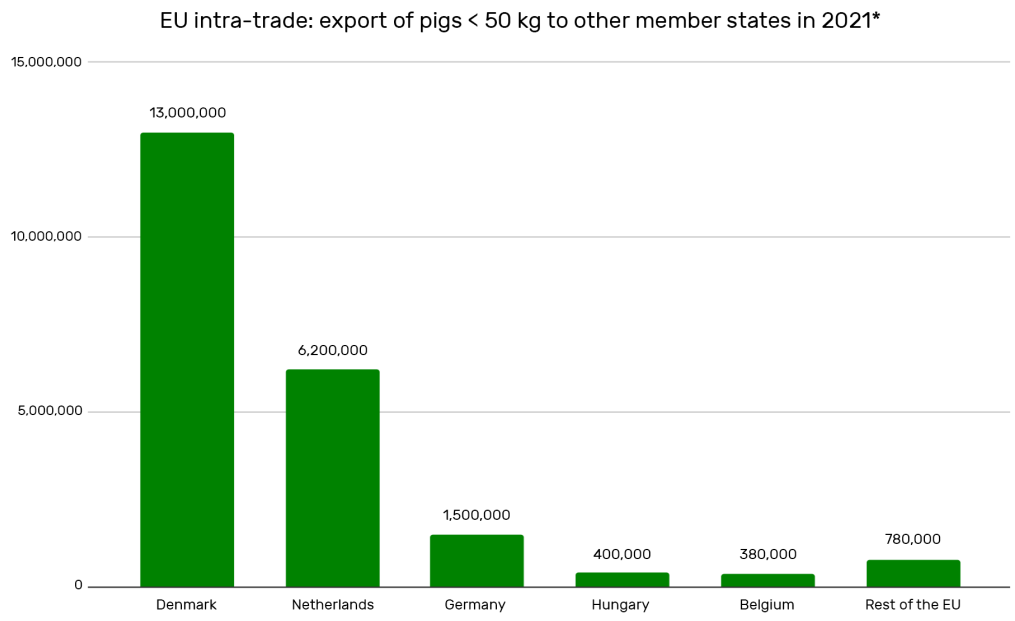
In the EU's trade statistics, piglets are not registered per head, but their total weight shipped across intra-European borders in kilograms. In addition to different recording systems of animal transports in the EU member states, this can lead to statistical inaccuracies. Moreover,

the common statistics of the EU member states only ever reflect the national statistics. For example, country A may state that it exports product X in the amount of 1,000 tonnes to country B. This is not always the case. While in the national statistics of country B it is stated that product X in the amount of 900 tonnes is imported from country A. This always leads to inaccuracies. According to all empirical values, the aggregated statistics do not reflect the flow of goods in detail, but on the whole, they do reflect it well. For these reasons, however, the figures have been roughly rounded.

In the following movement figures of live piglets in the EU, the authors have taken a piglet to be 30 kilograms, even though in reality they often weigh less, for example 25 kilograms. 1000 kilograms of transported piglets are equated with 33 piglets, but in reality, it could also have been 40 animals. The following animal numbers are therefore very conservatively estimated and could be even higher in reality.

4.3.3. MOVEMENT OF PIGLETS WITHIN THE EU

In 2021, according to EU trade statistics, 613,597 tonnes of pigs under 50 kilos live weight were moved across national borders within the EU. This should therefore have involved around 20.5 million piglets. By far the largest exporters were Denmark with about 13 million animals and the Netherlands with about 6.2 million animals. Germany follows in third place with about 1.5 million exported piglets. Hungary is in fourth place with about 400,000 and Belgium in fifth place with a good 380,000 animals. However, the figures given for Hungary are contradictory in the various query parameters of the database used.

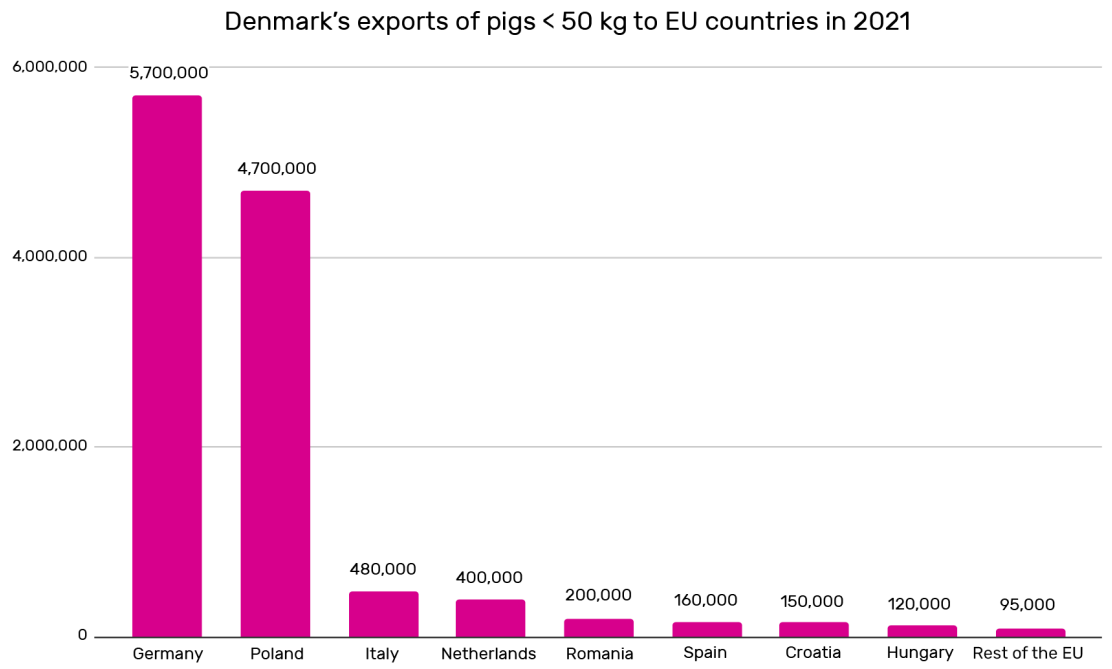


*Export figures for Cyprus were not yet available at the time of the query

Germany is not only the third largest exporter of piglets in the EU, but is even in the lead in terms of imports, followed by Poland, Spain, Italy, Romania, Belgium and the Netherlands.

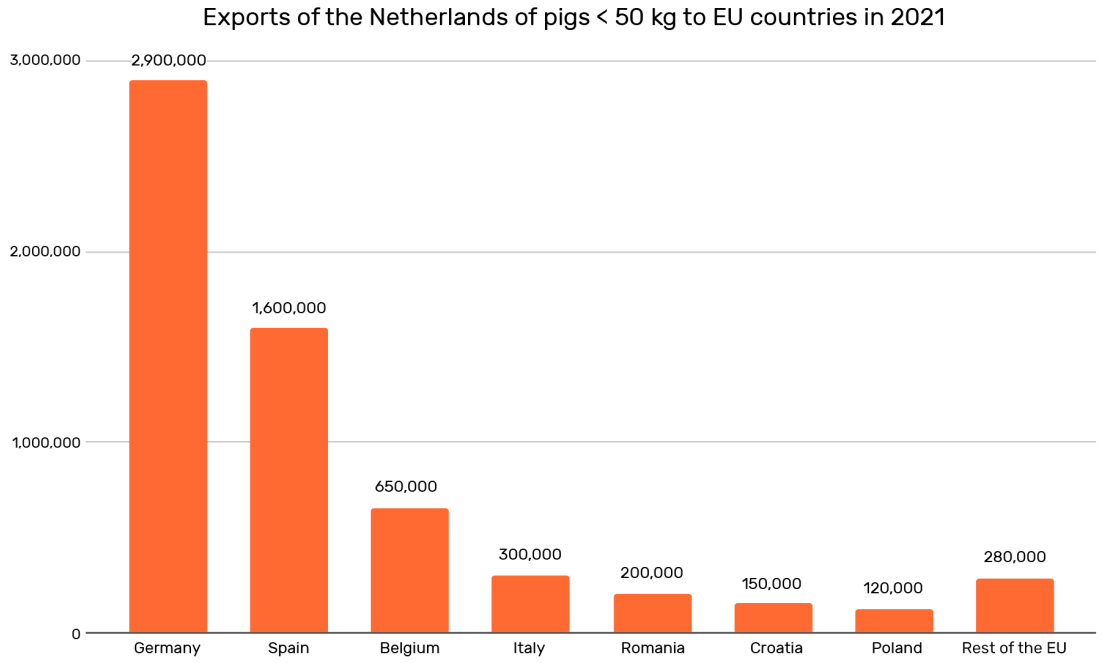
Since, in addition to the conditions in the livestock transporter, the length of the transport route plays a decisive role in the health impact on the piglets during transport, we look at the destination countries of the transports for Denmark and the Netherlands.

4.3.4. DANISH EXPORTS



Denmark exports piglets mainly to its neighbouring countries Germany and Poland. However, exports in the six-digit range also go to countries at a considerable distance from Denmark.

4.3.5. DUTCH EXPORTS



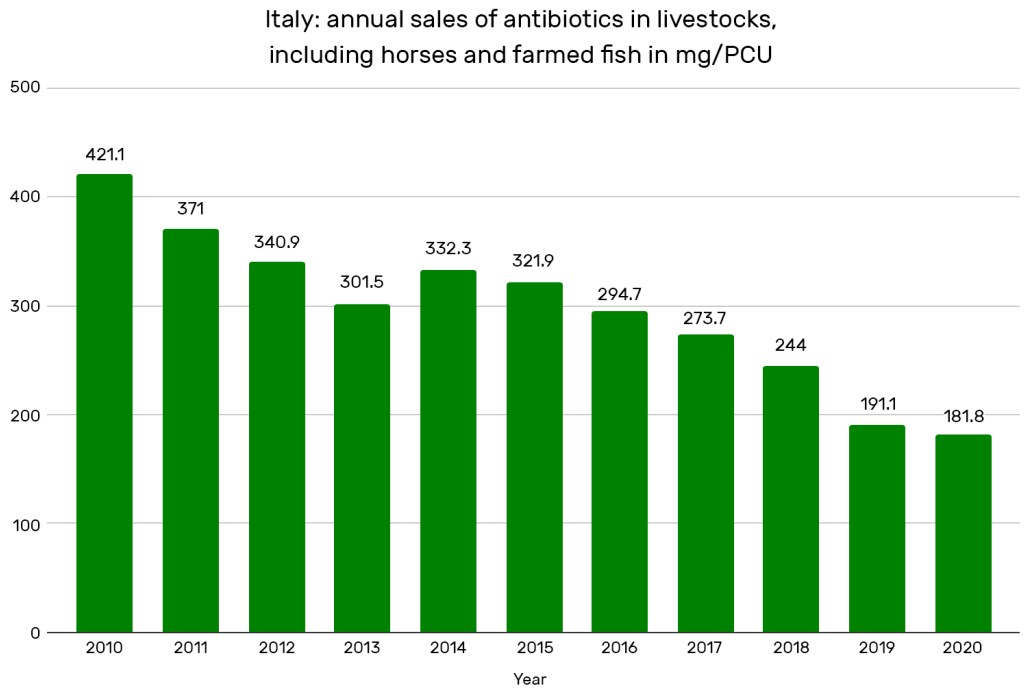
Besides the neighbouring countries Germany and Belgium, the Netherlands also supplies Spain with almost 1.6 million piglets. Piglets for Italy, Romania and Croatia are also sent on longer routes.[52]

4.4. ANTIBIOTIC CONSUMPTION AND STRATEGY IN COUNTRIES WITH HIGH CONSUMPTION, USING ITALY AS AN EXAMPLE

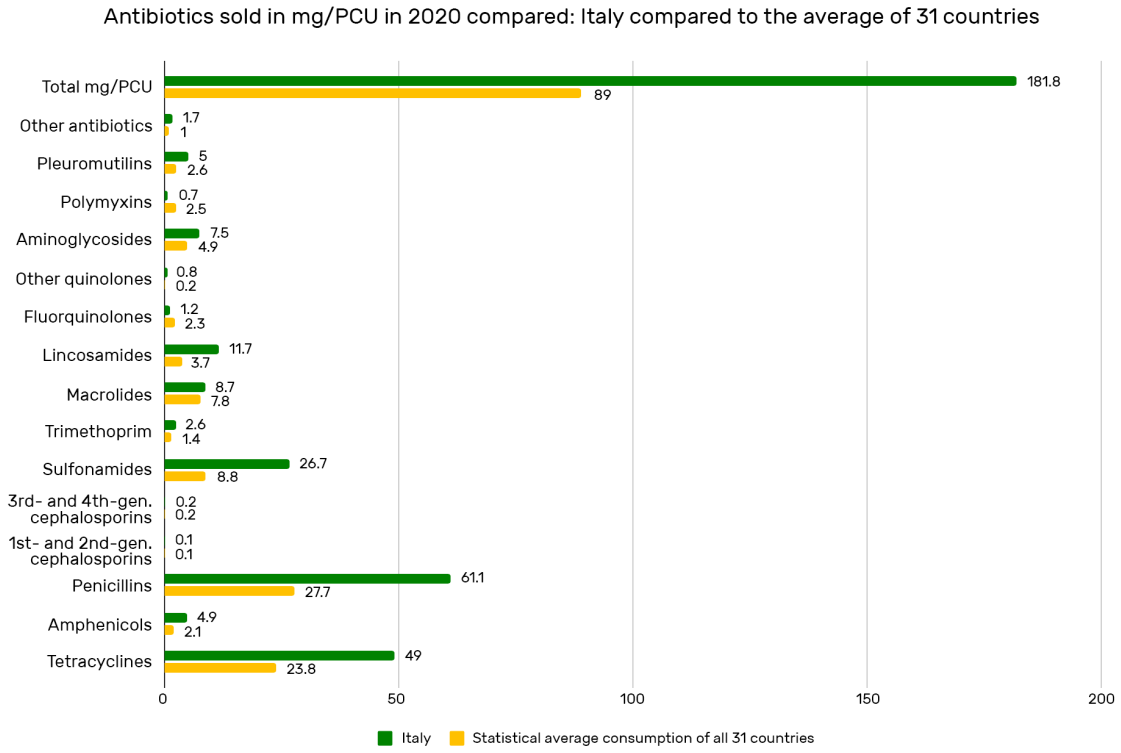
4.4.1. DATA ON ANTIBIOTIC USE

According to the 11th ESVAC Report, Italy was the country with the highest sales of antibiotics in mg/PCU in the fattening and keeping of farm animals in 2010, with 421.1 mg/PCU. In the years up to 2020, there was a virtually steady reduction in the sale of antibiotics in the veterinary sector.

52 All statistical data from: https://trade.ec.europa.eu/access-to-markets/en/statistics



In 2020, the sale of antibiotics in Italy had more than halved to only 181.8 mg/PCU, but Italy was still high in the list of EU countries reporting to ESVAC with this value. In 2020, only Cyprus (391.3 mg/PCU) and Poland (187.9 mg/PCU) had reported levels above those of Italy. Other countries with high pig production such as Spain with 154.3 mg/PCU or Poland (126.3) were below the Italian values or undercut them more than significantly such as Germany (83.3), France ((56.6) the Netherlands (50.2) or Denmark with only 37.2 mg PCU.[53]



53 "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, pages 51-52 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf

In total figures, Italy with 181.8 mg/PCU was above the average value of 89.0 mg/PCU of the 31 reporting countries by a factor of 2. For tetracyclines the factor was 2.1, for penicillins 2.2, for sulfonamides 3 and for lincosamides Italy was above the median consumption by a factor of 3.2.[54]

4.4.2. ITALIAN NATIONAL ACTION PLAN

With the agreement on a national action plan on antimicrobial resistance on 2 November 2017 "Piano nazionale di contrasto dell'antimicrobioto-resistenza (PNCAR) 2017-2020", Italy is trying to reduce the high level of antibiotic use. The plan has a "One Health" approach. It is therefore not only about the administration of antibiotics in veterinary medicine, but also about the use of antibiotics in human medicine.

The four goals relating to veterinary medicine for the target year 2020 are explained below.

- By 2020, the use of antibiotics in livestock farming should be reduced by more than 30%.
- The use of antibiotics classified by the WHO as "Critically Important Antimicrobials (CIA)" should be reduced by more than 10%.
- The administration of colistin should be reduced to 5 mg/PCU.
- The oral administration of antibiotics to livestock via feed premixes, drinking water or other oral presentations should be reduced by more than 30%.[55]

The most important building block for achieving these goals is the newly introduced digital recording of all antibiotic prescriptions for livestock and pets. In this way, the authorities are to obtain a complete overview of which antibiotics are administered to which animals in which livestock farms and for what reasons, and no longer just the sales figures for antibiotics as the basis for the use of the substances in Italy. By comparing the data collected by the authorities on carcass findings and detected resistances, the aim is to identify the livestock farms that pose a particularly high risk for the spread of resistances.

Three of the four goals were achieved within the planned timeframe.

- The use of antibiotics in livestock farming was reduced by 33.7%.
- The use of Critically Important Antimicrobials (including Highest Priority CIA) was reduced by 32%.

54 Ibidem page 29

55 PNCAR, National Action Plan on Antimicrobial Resistance 2017 - 2020 https://www.salute.gov.it/portale/antibioticoresistenza/dettaglioContenutiAntibioticoResistenza.jsp?lingua=italiano&id=5281&area=antibiotico-resistenza&menu=vuoto

- The administration of colistin could be reduced to 0.7 mg/PCU.[56]
- However, the oral administration of antibiotics in animal husbandry remained practically unchanged at a good 90 % of all administrations.[57]

With the exception of the critical oral administration of antibiotics to livestock, Italy was able to achieve the set goals, but is still far ahead in total numbers in a European comparison. There have been various scientific publications on the possible reasons for this in recent years.

4.4.3. ROLES AND POSITIONS OF ITALIAN VETERINARIANS

On 25 August 2020, the Italian Journal of Animal Science published the technical report "Antimicrobial use and antimicrobial resistance standpoint and prescribing behaviour of Italian cattle and pig veterinarians".[58]

The aim of the study was to identify existing knowledge gaps among veterinarians on antibiotic prescriptions and the reasons for them, to analyse possible different views of cattle and pig veterinarians and their habits on antibiotic prescribing, and to learn about their views on alternative treatments.[59]

Between September and November 2017, 789 Italian veterinarians were interviewed via WEB survey.[60] According to their own statements, 422 of them were mainly involved in the care of cattle and 96 were mainly involved in the care of pig farms. Almost 86% of the veterinarians from cattle farming were male and a good 56% had been working in their profession for more than 20 years. The quota of men among the veterinarians in pig husbandry was just under 80%, and a good 54% stated a length of service of more than 20 years.[61]

Almost 86% of the veterinarians working in cattle farming agreed with the statement that the preventive prescription of antibiotics in cattle farming promotes the development of antibiotic resistance. However, almost 84% also believe that alternative methods such as homeopathy or phytotherapy cannot replace antibiotics. Thus, despite the high awareness of the dangers of preventive antibiotic prescriptions, only a good 64% of them stated that they also recommend alternative treatment methods. Among the veterinarians working in pig farming, only just under 70% were of the opinion that preventive antibiotic administration promotes antibiotic resistance. As many as 69.1% stated that they also recommend alternative

56 "Sales of veterinary antimicrobials agents in 31 European countries in 2017"; Ninth ESVAC report, 15 October 2019, page 25 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2017_en.pdf and "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, page 29; Own comparative calculation https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf

57 "Sales of veterinary antimicrobials agents in 31 European countries in 2017"; Ninth ESVAC report, 15 October 2019, page 29 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2017_en.pdf and "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, page 34

58 G. Pozza, A. Pinto, S. Crovato, G. Mascarello, L. Bano, M. Dacasto, A. Battisti, B. Bartoli, L. Ravarotto & S. Marangon (2020) Antimicrobial use and antimicrobial resistance: standpoint and prescribing behaviour of Italian cattle and pig veterinarians, Italian Journal of Animal Science, 19:1, 905-916

59 Ibidem page 906

60 Ibidem page 906-907

61 Ibidem page 908

methods of treatment, although again 74% do not see these methods as an alternative.[62] It seems that veterinarians tend to prescribe the alternative uses under pressure from the public or on demand from animal owners, without being convinced of their benefits.[63]

Almost 77% of those working in cattle farms agreed with the statement that too much antibiotics are used in rearing facilities, the same percentage stated that antibiotic resistance is a relevant problem in Italy. Similarly, 75% of veterinarians working in pig farms saw excessive use of antibiotics, 72% saw this as a relevant problem.[64] It is noteworthy that among the veterinarians working in cattle farms, a good 53% stated that antibiotic administration to farm animals in the farms in which they themselves worked was not always in accordance with national and European guidelines. Among the veterinarians working in pig farms, the figure was just under 49%.[65]

At the same time, awareness of the negative effects of antibiotic use seems to be very high among both groups. Among veterinarians working in cattle farming, 86% said they agreed with the statement that inappropriate administration of antibiotics has a negative impact on animal health. At the same time, almost 87% see negative consequences for human health. Among those working in pig farms, the corresponding figures of a good 83 and 80% show a similarly high awareness of the possible dangers.[66]

The authors of the study suspect that external factors such as the wishes of the owners to the veterinarians, the simplicity of prescriptions, the price of the drugs and other economic factors may influence the behaviour of the veterinarians.[67]

4.4.4. ANTIBIOTIC USE IN THE FATTENING OF ITALIAN "HEAVY PIGS"

On 10 December 2020, a study on the use of antibiotics in Italian heavy pig production farms was published in the journal "Antibiotics" by the Swiss publisher MDPI: "The Use of Antimicrobials in Italian Heavy Pig Fattening Farms".[68] The data collected is from the year 2015.[69]

"Heavy pigs reach a slaughter weight of 150 kilograms and higher.[70] This is very high in European comparison. Pigs in Germany, for example, reach an average slaughter weight of around 100 kilos.[71] World-famous Italian specialities such as Parma or San Daniele ham are produced from these heavy pigs.[72]

62 Ibidem page 905+909
63 The authors
64 Ibidem page 909
65 Ibidem page 912
66 Ibidem page 909
67 Ibidem page 912
68 "The Use of Antimicrobials in Italian Heavy Pig Fattening Farms", Antibiotics 2020, 9, 892; doi:10.3390/antibiotics9120892 https://www.mdpi.com/2079-6382/9/12/892/htm
69 Ibidem page 1
70 Ibidem page 1
71 https://de.statista.com/statistik/daten/studie/163421/umfrage/schweine---schlachtgewicht/#:~:text=With%20a%20weight%20of%20an%20average,2021%20slaughtered%20in%20German%20butcheries
72 https://www.mdpi.com/2076-2615/11/6/1690

All 143 farms surveyed had a minimum of 1,000 fattening places for pigs from 20 to 30 kilos and fattened until they reached slaughter weight. This was 169 kilos on average. The average number of fattening places was 4,679 animals. The smallest fattening farm had 1,014 fattening places, the largest 43,159. A total of 916,276 pigs were fattened on the participating farms in 2015.[73] All participating farms were located in the northern regions of Piedmont, Lombardy, Emilia-Romagna and Veneto. These regions account for around 85% of all the approximately 11 million pigs slaughtered in Italy each year.

The data on antibiotic use in the fattening farms were collected through visits to the farms between June 2016 and December 2017. All 143 fattening farms were also participants in the development of the Classy Farm System of the Italian Ministry of Health from 2016 to 2017. In addition, all 143 fattening farms had previously been involved in health programmes of the competent local veterinary authority "Istituto Zooprofilattico Sperimentale Lombardia Emilia Romagna's" (IZSLER), which is also subordinate to the Ministry of Health.[74]

On average, 4% of the fattened pigs died during the fattening process. In 93.7% of the 143 farms, HPCIA antibiotics were used during fattening. The share of HPCIA in all antibiotics used was 16.8%.

On median, antibiotics were given on 10.7 out of 100 fattening days. The range of the value within the 143 farms was very high and lay between 0.2 and 49.5.[75] 10.7 is a high value. This value was 2 days in Denmark in 2015.[76] The median for the use of HPCIA was 1.5 days. There was also a high range for HPCIA between 0.0 and 18.0.

94.6% of all antibiotic administrations in the fattening farms did not take place as individual but as group treatment and by oral route.[77]

The more animals were housed on the farms, the fewer antibiotics were administered on average. At the same time, the number of group treatments in the large farms was higher than in the smaller ones.[78] According to the authors of the study, the fact that fewer antibiotics were used on average on larger fattening farms could be due to the fact that herd management and biosecurity issues receive more attention on larger farms. As high doses of antibiotics during fattening do not seem to have a significant influence on the mortality of pigs, the authors recommend further studies on the influence of fattening management, biosecurity and the husbandry system on farms and on the use of alternatives to antibiotics.[79]

73 Ibidem page 2
74 Ibidem page 7
75 Ibidem page 2
76 Ibidem page 6
77 Ibidem page 2
78 Ibidem pages 4-5
79 Ibidem pages 6-7

4.4.5. HISTORICAL, SOCIAL AND ECONOMIC BACKGROUND FOR ANTIBIOTIC USE IN PIG FATTENING: COMPARISON BETWEEN ITALY AND SWEDEN

On 14 July 2021, the journal Humanities & Social Sciences Communications published the article "Antibiotics in pork production: restrictions as the exception and excessive use as the norm? Experiences from Sweden and Italy". The data used refer to the year 2018.[80]

The comparison lends itself to the fact that Italy led the EU countries (except Cyprus) in 2018 with a use of 244 mg/PCU of antibiotics, while Sweden was the country with the lowest use at 12.5 mg/PCU.

4.4.5.1. SWEDEN

Already in 1986, 20 years before the EU in 2006, Sweden had banned the use of antibiotics as performance enhancers in animal fattening and thus also the routine administration in the feed and water of the animals. Before this ban, the average Swedish use was around 50 mg/PCU.

In Sweden, environmental problems, also triggered by agricultural practices, were already being discussed by the general public in the 1960s. An environmental protection agency, the first of its kind, was established in Sweden in 1967, and in 1972 Sweden hosted the first United Nations Global Conference on the Environment.[81]

A high level of awareness among the population about hygiene measures in livestock farming was also beneficial. After a nationwide outbreak of salmonella in Sweden in 1956, which resulted in numerous illnesses and deaths, a strict salmonella control programme was introduced. This was initially financed by the Swedish state and continues consistently to this day, but is now financed by all those involved in the production process. Since then, Sweden is considered to have a very low incidence of salmonella.[82]

Questions such as "What will happen to the soil in the long term if we spread manure from animals whose feed contains antibiotics?" were raised by representatives of the Swedish Farmers' Union. The first draft for a voluntary ban on antibiotics as a normal feed ingredient did not come from the authorities in 1981, but from the Swedish Farmers' Association. In 1988, a law on animal welfare was passed in Sweden that ensured farm animals not only freedom from suffering, but also a right to health, in addition to enabling species-appropriate behaviour. New hygiene systems in livestock farms, vaccinations and other disease prevention measures were established. The use of antibiotics dropped from 50 mg/PCU in the early nineties to 30 mg/PCU. It then dropped from the mid-nineties to the current 11-12 mg/PCU. In Sweden, only about 10% of all antibiotic doses to farm animals are administered as group treatments. In Italy, this figure is 90%.

80 Antibiotics in pig meat production: restrictions as the odd case and overuse as normality? Experiences from Sweden and Italy, Humanities and Social Science Communications; (2021) 8:172, https://doi.org/10/1057/s41599-021-00852-4

81 Ibidem pages 2-6

82 Salmonella control in the EU and in Germany with special regard to organic livestock farming, Thomas Blaha, University of Veterinary Medicine Hanover Foundation, Branch Office for Epidemiology, Büscheler Str. 9, D-49456 Bakum, page 49 https://literatur.thuenen.de/digbib_extern/dk040450.pdf

But the expectations of the pioneers that the changes in livestock farming would lead to a market advantage were not fulfilled. Sweden's accession to the EU in 1996, and with it the opening of the market for meat produced in other European countries, had major consequences. Swedish consumers switched to pork from other EU countries, which was 20-30% cheaper. While 4 million pigs were fattened annually in Sweden before EU accession, from then on the figure was only about 2.6 million. One consequence was a restructuring of the Swedish fattening farms. The small to medium-sized pig farmers gave up, while the large farms increased the number of fattening places and their production volume.

A turning point came in 2014, when several outbreaks of MRSA occurred in neighbouring Denmark, which attracted a lot of attention from the Swedish media. The use of antibiotics in animal fattening was again widely discussed in public. As a result, the major Swedish grocery chains announced that they would only accept meat from suppliers who did not use antibiotics for precautionary reasons in fattening. At the same time, a campaign on "Meat from Sweden" was launched, which also provided information on the, in contrast to many other European countries, extremely restrictive use of antibiotics in animal husbandry. Although Swedish pork is still 0.20 to 0.30 euros more expensive than imported meat for consumers, there has been a lasting change in purchasing behaviour since then.[83]

4.4.5.2. ITALY

In Italy, according to the analysis of the study authors, public debate on environmental policy took place to a much lesser extent than in Sweden. The focus of public discussions was more on social justice and the struggle for workers' rights, and environmental debates were also conducted more from a left-wing perspective. Ecology was seen as a middle-class issue, and animal welfare was seen as an upper-class issue. Discussions about the use of antibiotics in human medicine and livestock farming took place in the academic milieu, but detached from environmental protection and mainly under medical aspects. The discussion rarely reached the public media.

In the absence of an intensive public debate, pressure for a different approach to antibiotic resistance only built up as a result of EU requirements. As recently as 2017, staff from the European Centre for Disease Prevention and Control (ECDC) wrote after a visit to Italy: “During conversations in Italy, ECDC often gained the impression that these high levels of AMR appear to be accepted by stakeholders throughout the healthcare system, as if they were an unavoidable state of affairs.”

It was not until the end of 2017, with the introduction of the "Piano nazionale di contrasto dell'antimicrobioto-resistenza" (PNCAR), that media interest in the problem of antibiotic resistance in human and veterinary medicine grew. Financial resources were made available for research into antibiotic resistance in farm animal husbandry, exclusively digital prescriptions were introduced in veterinary medicine and thus an essential basis for recording the overall situation in farm animal husbandry was created. But so far there has been no legal ban on the

83 Antibiotics in pig meat production: restrictions as the odd case and overuse as normality? Experiences from Sweden and Italy, Humanities and Social Science Communications; (2021) 8:172, pages 2-6 https://www.nature.com/articles/s41599-021-00852-4.pdf

purely prophylactic administration of antibiotics in livestock farming. Animal products may be labelled "antibiotic-free" if the animals have not been treated with antibiotics in the last four weeks before slaughter.

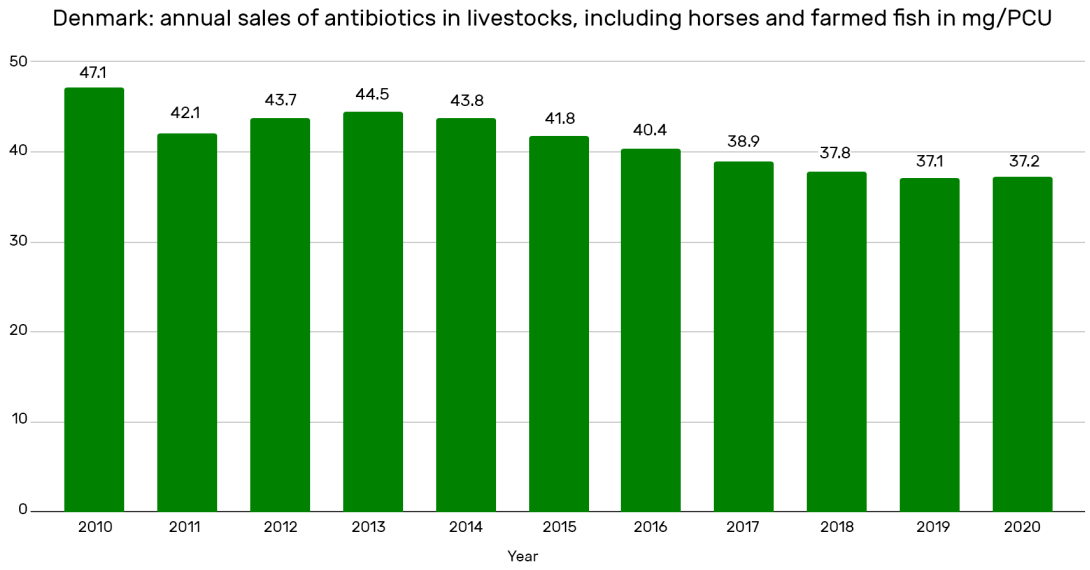
In the social media, too, the use of antibiotics in livestock farming is primarily discussed in terms of the involuntary intake of antibiotics by humans through the consumption of animal products; the problem of resistance in bacteria is less in focus. The fatteners of heavy pigs in northern Italy also shy away from participating in the public discussion or try to avoid it. The image campaign for Italian meat products such as Parma ham focuses on the end product and only little on its production. Since 40% of the Heavy Pigs' products are exported, there is also an interest in not jeopardising these exports by loud domestic discussions on the use of antibiotics.

In addition to these society and sociological based aspects, the Italian husbandry system is predominantly oriented towards compliance with EU regulations on pig husbandry. Voluntary services with regard to animal welfare are not established. Pig production in Italy is mainly based on specialised housing systems. As is often the case in other EU countries with a large pig fattening sector, the animals are transported from farms for piglet production to farms for intermediate fattening and from there to farms for final fattening. Not only are the animals repeatedly mixed with pigs from other farms, which can lead to mutual transmission of diseases, but the transports alone are stressful for the animals and can also lead to injuries to the animals during loading, unloading and transport. In the final fattening stage, the animals have few opportunities to behave in a manner appropriate to their species, which leads to stress and thus to a higher susceptibility to diseases, which in turn are cured with antibiotics, which are administered more frequently than in other European countries.

At the same time, the existing system has been well-rehearsed between all parties involved for decades, is economically successful and - presumably also due to a lack of knowledge about the production conditions - widely accepted by the consumers of the Heavy Pigs' products.[84]

84 Antibiotics in pig meat production: restrictions as the odd case and overuse as normality? Experiences from Sweden and Italy, Humanities and Social Science Communications; (2021) 8:172, pages 6-10 https://www.nature.com/articles/s41599-021-00852-4.pdf

4.5. ANTIBIOTIC CONSUMPTION AND STRATEGY IN LOW-CONSUMPTION COUNTRIES USING THE EXAMPLE OF DENMARK



4.5.1. DATA ON ANTIBIOTIC USE

With a sale of 37.2 mg/PCU antibiotics in 2020, Denmark is clearly below the European average value of 89 mg/PCU.[85] In 2010, Denmark was already in the lower range with 47.1 mg/PCU compared to other EU countries with intensive animal husbandry. In 2017, at 38.9 mg/PCU, the value fell below 40 mg/PCU for the first time, and there have been no significant reductions since then.[86]

4.5.2. INTENSIVE CONVENTIONAL PIG PRODUCTION

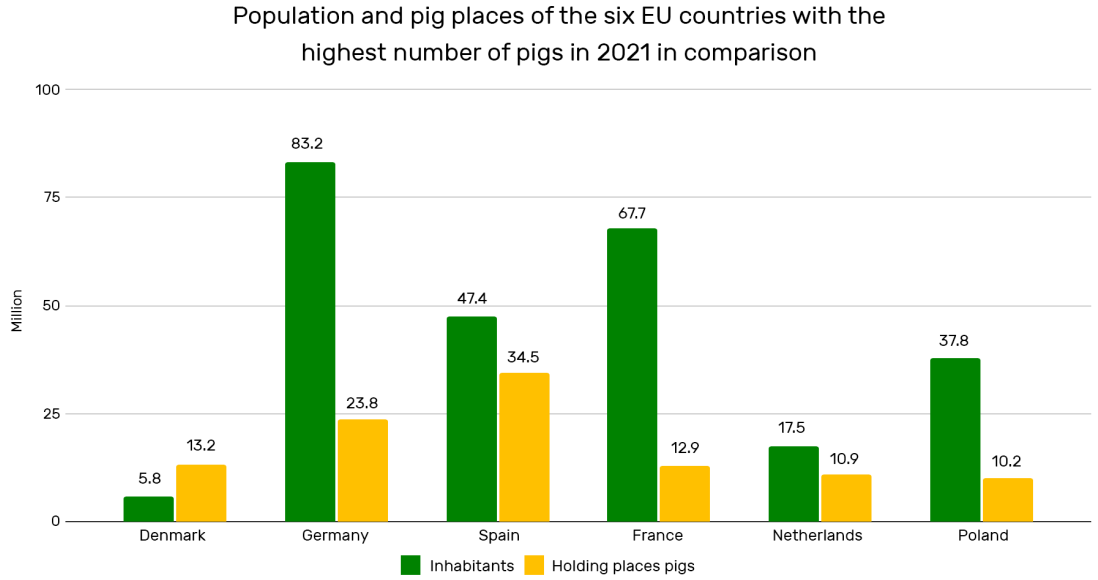
The low consumption of antibiotics in the years 2010 to 2020 is striking against the background that Denmark has the highest number of pigs in the EU compared to the number of inhabitants. In 2020, Denmark had just under 13.4 million pigs with a population of 5.82 million. France has more than eleven times as many inhabitants as Denmark, with practically the same number of places.

In Denmark there are 2.28 pig places per inhabitant, in Spain 0.73, in the Netherlands 0.62, in Germany 0.29, in Poland 0.27 and in France 0.19 places per inhabitant. Denmark is thus the

85 "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, page 29 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf

86 Ibidem page 51-52

largest producer of pigs in the EU in relation to the number of inhabitants.[87] Around 75% of all antibiotics prescribed in livestock farming in Denmark were used in the pig farming sector in 2020.[88]



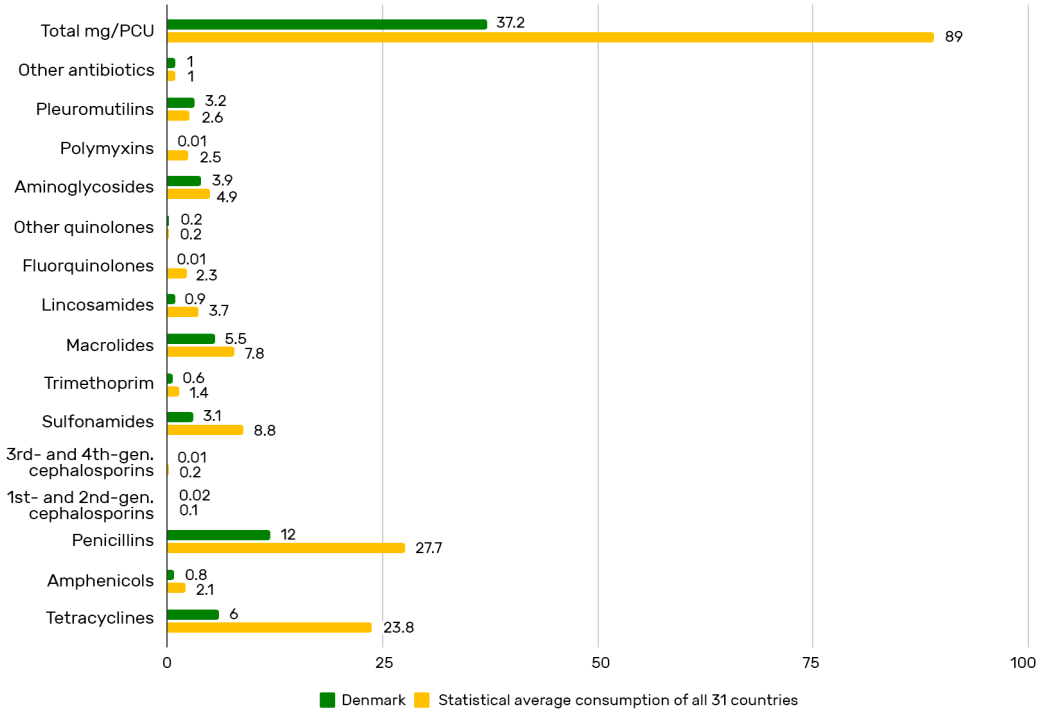
Denmark is in a particularly good position with regard to the use of antibiotics designated as HPCIA. For cephalosporins of the 3rd and 4th generation, for fluoroquinolones and polymyxins, a use of less than 0.01 mg/PCU is given. Only for macrolides is a value of 5.5 mg/PCU given. However, even this value is still well below the average value of 7.8 mg/PCU of the countries reporting to ESVAC.[89]

87 Own calculations

88 DANMAP 2020 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark; Page 45 https://www.danmap.org/reports/2020

89 Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, page 29 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf

Antibiotics sold in mg/PCU in 2020 compared: Denmark compared to the average of 31 countries*



*The values for polymyxins, fluoroquinolones and 3rd and 4th generation cephalosporins are reported by ESVAC as <0.01 mg/PCU.[90]

4.5.3. DANMAP - THE DANISH WAY SINCE 1995

4.5.3.1. PREHISTORY

After resistance to antibiotics was repeatedly detected in farm animals in the 1960s, the suspicion arose that this resistance could be related to the use of antibiotics as so-called performance promoters (Animal Growth Promoter AGP), that these bacteria could exchange the acquired resistance among themselves and thus also become a risk in the treatment of bacterial diseases in human medicine. In 1969, this connection was considered proven in Great Britain. As a result, antibiotics used in human therapy were banned in the UK for use as AGPs in livestock. With the UK's entry into the EU in 1972, this ban was adopted for all member countries.

But the discussion at the time overlooked the fact that different antibiotics belonging to the same class of active ingredients can acquire the same resistances. The fact that antibiotics, which were used exclusively as AGPs in animal fattening at the time, could one day become important for the treatment of antibiotic resistance in human medicine was also not part of the scientific discussion at the time.

90 Note by the authors

In 1993, enterococci resistant to the antibiotic vancomycin were isolated in farm animals in England. Vancomycin belongs to the antibiotic group of glycopeptides and until then had not been approved for use in veterinary medicine in either England or Germany. However, the glycopeptide avoparcin had an authorisation as AGP in animal fattening. After a random sample in Danish broilers in December 1994, these resistances were also detected in Denmark in January 1995 and a connection with the use of avoparcin as an AGP, which was also approved in Denmark, seemed obvious.

In Denmark, there has been an increasingly critical discussion about the use of antibiotics in livestock farming since the beginning of the 1990s.

Thus, the new findings met with lively scientific as well as public interest. As early as April 1995, the Danish agricultural associations declared a voluntary renunciation of the use of avoparcin as an AGP, followed a month later by a ban by the Danish Ministry of Agriculture. But the central authorisation body for AGP within the EU (Scientific Committee on Animal Nitrition, SCAN) opposed a ban on avoparcin. Denmark would only be able to maintain the ban if it could present new evidence that the use of avoparcin in livestock posed a risk to human health through possible transfer of resistance. Denmark then established DANMAP (Danish Integrated Antimicrobial Resistance Monitoring and Research Programme) in 1995. After the scientific evidence for the suspected transfer of resistance became stronger, the use of avoparcin in livestock was banned throughout the EU in 1997.

It was helpful for all these projects that the "Danish Specific Patogen Free System (SPF System)" has existed in Denmark since 1971. This system was set up by the Danish Agriculture & Food Council (DAFC) and records important typical diseases that can occur in pig herds, such as mycoplasmosis, pleuropneumonia and mange, as well as louse infestation and the salmonella status of individual herds. The main purpose of the system is to prevent the introduction of new diseases into pig herds when animals are transported from piglet producers to weaner fatteners and on to finishing fatteners, thereby mixing with animals from other herds. The health status of individual herds is publicly available and is also basic information for veterinarians and other visitors to pig farms. According to the DAFC, around 75% of all pigs born in Denmark were covered by the SPF system in 2018.[91]

4.5.3.2. IMPLEMENTATION

DANMAP is funded interdepartmentally by the Ministries of Agriculture, Health and Science. The annual reports are jointly produced by the National Institute for Serum Analysis (Statens Serum Institut), the National Institute for Animal Health (DTU Vet) and the National Institute for Food Safety (DTU Fødevareinstituttet).

From 1995 onwards, resistance was initially investigated in food-producing animals and from 1996 onwards the investigation programme was extended to food and humans.[92]

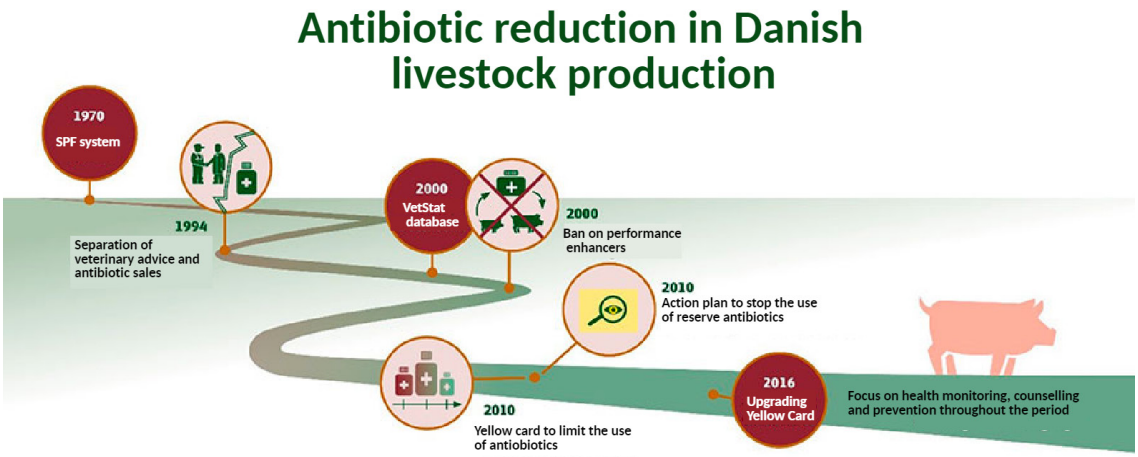
91 FAO and Denmark Ministry of Environment and Food - Danish Veterinary and Food Administration. 2019. Tackling antimicrobial use and resistance in pig production: lessons learned from Denmark, page 4-5 https://www.fao.org/3/ca2899en/ca2899en.pdf

92 DANMAP 2015 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark; pages 10-11 https://www.danmap.org/reports/2015

Since there was information on the total use of antibiotics in livestock farming in Denmark in the 1990s, but no overview of which antibiotics were given to which animals of which age for which purpose over which period of time, VetStat was also introduced in 2000. VetStat records all antibiotic use and prescriptions to farm animals in Denmark.[93]

DANMAP is a surveillance system with five key objectives:

- To establish the state-of-nation in regards to the use of antimicrobial agents in food animals and humans
- To carry out surveillance of the occurrence of antimicrobial resistance in bacteria isolated from food animals, food of animal origin (e.g. meat) and humans
- To identify areas for further research e.g. transmission or regarding possible associations between antimicrobial consumption and antimicrobial resistance
- To deliver data to veterinarians, medical doctors and other health professionals for the development of antibiotic guidelines for treatment
- To act as a knowledge base for authorities, academia and politicians when performing risk assessment and management, thus supporting decision making in the prevention and control of resistant bacterial infections.[94]



Since the introduction of DANMAP to Danish livestock farming, the system has continued to develop.

93 FAO and Denmark Ministry of Environment and Food - Danish Veterinary and Food Administration. 2019. Tackling antimicrobial use and resistance in pig production: lessons learned from Denmark, page 10-11 https://www.fao.org/3/ca2899en/ca2899en.pdf

94 DANMAP 2020 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark; Page 14 https://www.danmap.org/reports/2020

4.5.3.3. DISPENSING OF VETERINARY MEDICINAL PRODUCTS

In 1995 there was also a significant change for Danish veterinarians. Following a change in national legislation, veterinarians were no longer allowed to make a profit from selling medicines to livestock farmers. At the same time, Veterinary Advisory Service Contracts (VASC) were introduced between livestock farmers and veterinarians.[95] The focus of the VASC is on health advice and prevention of diseases and not on their treatment. Antibiotics should only be used in a targeted manner and with a view to avoiding possible resistance.[96] On the basis of this VASC, veterinarians visit the farm animal herd under their care at least once a month and draw up a herd health plan. In return, the livestock farmers are allowed to stockpile medicines and use them independently according to the principles of the herd health plan. From 1995 onwards, VASC agreements were voluntary; since 2010, these agreements have been compulsory for all large pig and cattle farms as well as mink farms. In 2019, 95% of all pigs kept in Denmark were covered by a VASC.[97]

In 2003, a Veterinary Medicine Task Force was established, consisting of 15 veterinarians and two lawyers. This group investigates violations of the extensive prescription obligation for veterinary medical products and their use. This task force is guided by anomalies in the prescribing of medicines by veterinarians or also by frequent interventions in livestock farms, but also follows up on tips and complaints from citizens and other stakeholders.[98]

4.5.3.4. REGULATORY GUIDELINES

Since 1996, guidelines on the use of antibiotics in pig and cattle farms have been published by the National Institute of Animal Health of Denmark. In 2005, these guidelines were updated by the Danish Veterinary and Food Administration. This time, in addition to the National Institute of Animal Health, the Institute of Food Safety, the Association of Danish Veterinarians, experts from the scientific community, the Danish Veterinary Medicine Manufacturers Association and the Danish Agriculture & Food Council, which is supported by the Danish agri-food industry, were involved. A further update was carried out in 2013.[99]

As early as 2002, the use of fluoroquinolones, which belong to the class of Highest Priority Critically Important Antimicrobials (HPCIA), was subject to strict restrictions. A five-day use of fluoroquinolones was only allowed if an accredited laboratory could prove that no other antibiotics could be used to treat the disease.

In 2010, a system of "yellow cards" was introduced in Denmark. Pig and cattle farms that exceed the thresholds for antibiotic use recommended in the guidelines are required to reduce antibiotic use within nine months. These farms will also receive an unannounced

95 FAO and Denmark Ministry of Environment and Food - Danish Veterinary and Food Administration. 2019. Tackling antimicrobial use and resistance in pig production: lessons learned from Denmark, page 5-6 https://www.fao.org/3/ca2899en/ca2899en.pdf

96 https://www.foedevarestyrelsen.dk/english/Animal/AnimalHealth/Veterinary_medicine/Pages/default.aspx

97 FAO and Denmark Ministry of Environment and Food - Danish Veterinary and Food Administration. 2019. Tackling antimicrobial use and resistance in pig production: lessons learned from Denmark, page 5-6 https://www.fao.org/3/ca2899en/ca2899en.pdf

98 European Commission: Final Report of a fact-finding Mission carried out in Denmark, February 2016, DG (SANTE) 2016-8882-MR, page 16 https://www.foedevarestyrelsen.dk/SiteCollectionDocuments/Pressemeddelelser/2016/Final_Report_EU-Kommissionen_2016_USE_OF_ANTIMICROBIALS_IN_ANIMALS.pdf

99 Ibidem page 9

but chargeable visit from a state veterinarian and be at higher risk of further regulatory inspections. In addition, more frequent visits by the self-selected private veterinarian are required.[100] In 2016, the Yellow Card system was expanded to include the use of Critically Important Antimicrobials in pig farms.[101]

The prescription period and use of antibiotics for farm animals is limited to five days, with the exception of adult cattle.[102]

In 2013, a differentiated tax on veterinary products was introduced, with vaccines remaining tax-free. Narrow spectrum penicillins and other veterinary products were given an extra 0.8% tax, a 5.5% tax rate was placed on other antibiotics and all CIA antibiotics were given a 10.8% tax.[103]

All regulatory actions were accompanied by national action plans with targets to further reduce antibiotic use in food-producing livestock in 2005, 2010, 2015 and 2019.[104]

The agricultural associations also supported the measures adopted in Denmark to reduce the use of antibiotics, especially those considered critical. The Danish Poultry Farmers' Association had already renounced the use of cephalosporins in 2000 (class CIA). In 2010, the Danish Pig Farmers' Association declared a voluntary renunciation of 3rd and 4th generation cephalosporins, which belong to the HPCIA class. The Danish cattle farmers followed this voluntary renunciation in 2014.[105]

4.5.3.5. ONE HEALTH STRATEGY

In 2010, new and stricter guidelines on the use of antibiotics in pig farms were presented at the annual meeting of Danish veterinarians and published in May 2011, developed under the "One Health Principle". Not only was the greatest possible efficiency of antibiotics in use on animal farms considered, but the importance of antibiotics for human health also became the basis for the new guidelines.[106]

In 2013, the University of Copenhagen launched a four-year excellence programme, the University of Copenhagen Research Centre for Control of Antibiotic Resistance (UC-CARE). In the programme, human and veterinary doctors together with scientists from the social sciences and humanities from a total of 14 faculties research the prevention of resistance to antibiotics. Every year, more than 400 students of human and veterinary medicine take a compulsory course on antibiotic resistance in humans and farm animals.[107]

100 Ibidem page 12
101 DANMAP 2020 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark; Page 7 https://www.danmap.org/reports/2020
102 https://www.foedevarestyrelsen.dk/english/Animal/AnimalHealth/Veterinary_medicine/Pages/default.aspx
103 European Commission: Final Report of a fact-finding Mission carried out in Denmark, February 2016, DG (SANTE) 2016-8882-MR, page 5 https://www.foedevarestyrelsen.dk/SiteCollectionDocuments/Pressemeddelelser/2016/Final_Report_EU-Kommissionen_2016_USE_OF_ANTIMICROBIALS_IN_ANIMALS.pdf
104 DANMAP 2020 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark; Page 6-7 https://www.danmap.org/reports/2020
105 European Commission: Final Report of a fact-finding Mission carried out in Denmark, February 2016, DG (SANTE) 2016-8882-MR, page 5-6 https://www.foedevarestyrelsen.dk/SiteCollectionDocuments/Pressemeddelelser/2016/Final_Report_EU-Kommissionen_2016_USE_OF_ANTIMICROBIALS_IN_ANIMALS.pdf
106 DANMAP 2020 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark; Page 26-27 https://www.danmap.org/reports/2020
107 DANMAP 2017 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark; Page 48-49 https://www.danmap.org/reports/2017

In 2017, also based on the new knowledge gained from the programme, a revised One Health strategy was presented to achieve a further reduction in the use of antibiotics in both veterinary and human medicine.[108]

4.5.3.6. VETSTAT

The administration of antibiotics to farm animals has been centrally recorded in the VetStat database in Denmark since 2000. The name of the prescribing veterinarian, the livestock farm, the type and quantity of antibiotics prescribed, the type of farm animals, their age group, the diagnosed disease and the time of administration of the antibiotics are recorded in VetStat.

The system is linked to a register of all veterinarians practising in Denmark (VetReg) and a database of all livestock kept in Denmark (Central Husbandry Register CHR). The data obtained through VetStat is used by the Danish authorities for risk modelling, risk-based inspections and follow-up inspections to check for detected deviating consumption of antibiotics.

VetStat also allows farmers and veterinarians to compare the use of antibiotics on their own farms with the use of antibiotics on other farms and can provide information on how changes in feed use, housing structure and stocking density can reduce the use of antibiotics. VetStat is also used by the authorities to identify farms and veterinarians with high antibiotic use or with frequent antibiotic prescriptions.

However, the Danish authorities state that VetStat is dependent on the IT infrastructure in place in Denmark and is thus not readily available for use in other EU member states.[109]

4.5.3.7. MARKET STRUCTURE

Another key to the success of Danish pig production in reducing antibiotics is the fact that livestock farmers in Denmark are organised in strong cooperative associations. These cooperatives also own feed mills, slaughterhouses and dairies. This gives the farmers access to the preliminary stages of their production as well as to the final processing.

The efforts to avoid antibiotic resistance and to minimise the use of antibiotics in livestock farming also met with strong public interest from the very beginning. The willingness to talk between livestock farmers, processors, scientists and authorities thus led to broad support for the measures adopted.[110]

However, there has also been a drastic change in the logistics of Danish pig production in recent decades. In 1997, about 19,000 pig farms produced almost 11 million pigs annually. Many farms were fully integrated with sow management and piglet production up to final fattening. In 2017, the number of farms had declined to just over 3,000. The farms specialised

108 DANMAP 2020 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark; Page 34

109 Ibidem page 6-7

110 FAO and Denmark Ministry of Environment and Food - Danish Veterinary and Food Administration. 2019. Tackling antimicrobial use and resistance in pig production: lessons learned from Denmark, page VII https://www.fao.org/3/ca2899en/ca2899en.pdf

in sow management with piglet production, intermediate fattening of weaned piglets and final fattening until slaughter.

The remaining farms produced more than 32 million pigs, of which about 18 million were slaughtered in Denmark and 14 million were exported for final fattening, mainly to Poland and Germany. In total, 90% of Danish pig production goes to more than 120 different markets around the world. Due to the high dependence on exports, Danish pig production is dependent on access to as many markets as possible. This is also a driving force behind the efforts to reduce antibiotic use in Danish pig production.[111]

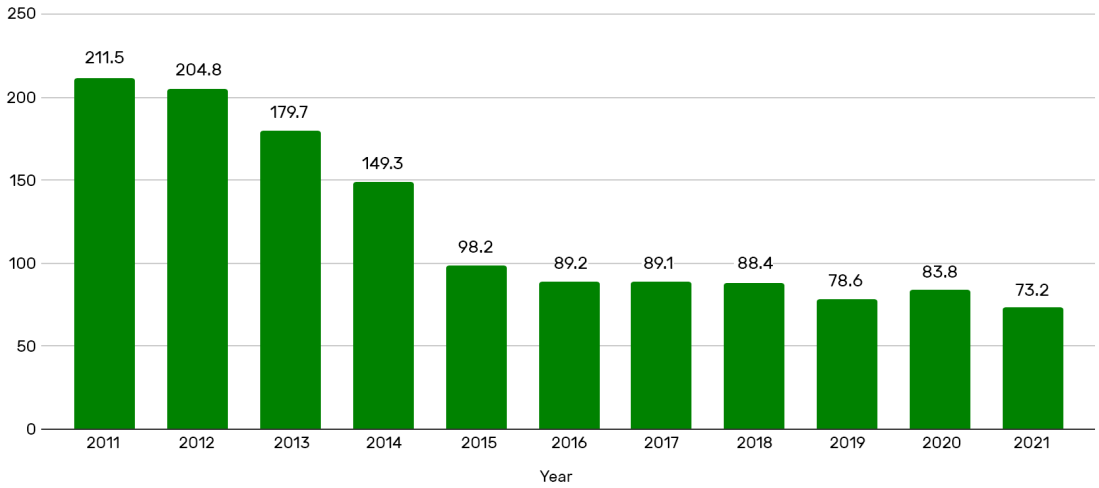
4.5.3.8. STRUCTURE VETERINARY MEDICINE

With this restructuring of pig farming and the strict and numerous regulatory requirements, there was also a transformation in Danish veterinary medicine. The veterinarians working in farm animal husbandry had to specialise more and more and were thus also able to acquire expertise in preventive medical treatment in their field. This also led to a concentration process in veterinary care. In 2018, there were only less than 10 large livestock practices in Denmark, which cared for practically all larger pig farms.[112]

4.6. ANTIBIOTIC CONSUMPTION AND STRATEGY IN GERMANY

According to the EMA, consumption in Germany declined significantly from the first report in 2011 and has settled at a medium level compared to the other European countries since 2016.[113]

Germany: annual sales of antibiotics in livestocks, including horses and farmed fish in mg/PCU

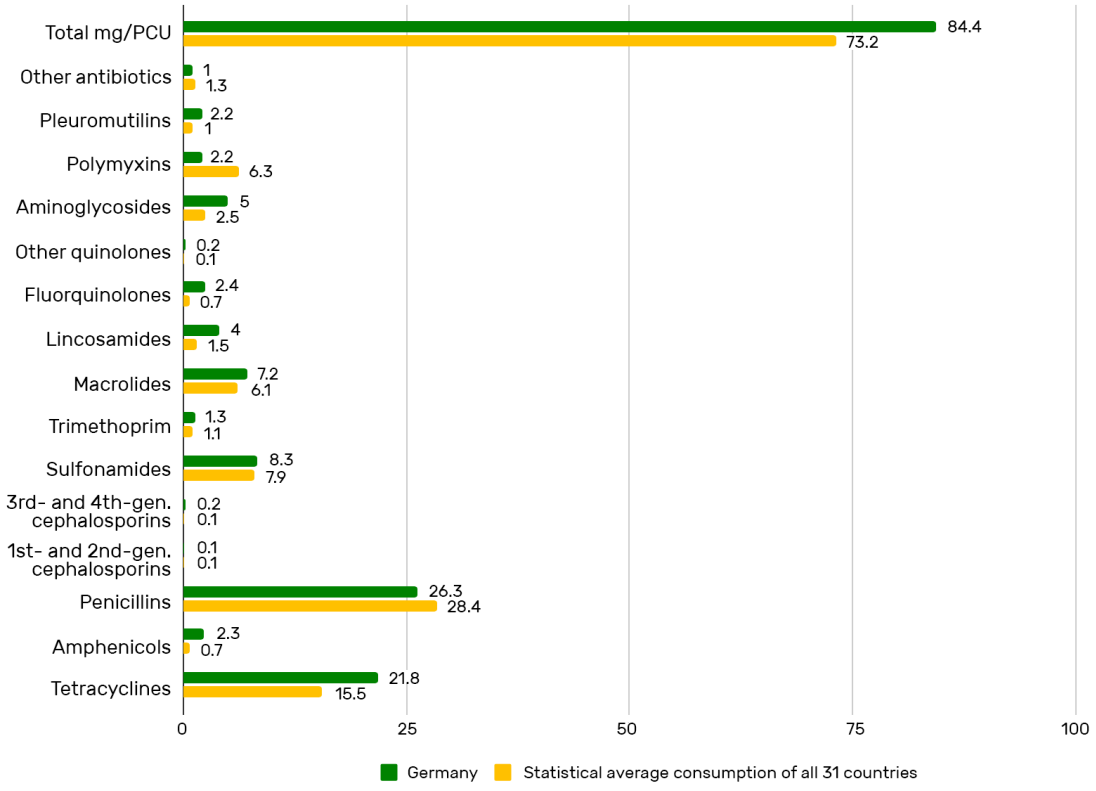


111 Ibidem page 1-3
112 Ibidem page 7
113 "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, pages 51-52 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf

In Germany, the quantities of antibiotics dispensed by pharmaceutical companies are recorded. In 2020, the Federal Office of Consumer Protection and Food reported an increase in the amount of antibiotics dispensed by 31 tonnes or 4.6 percent compared to the previous year. A total of 701 tonnes of antibiotics were dispensed, with penicillins (278 t) and tetracyclines (148 t) being the most commonly used, as in previous years. They are followed by sulfonamides (65 t), macrolides (61 t) and polypeptide antibiotics with 60 t.[114]

[115]

Antibiotics sold in mg/PCU in 2020 compared: Germany compared to the average of 31 countries



When looking at the groups of active substances (HPCIA) that are particularly decisive for human medicine, it is noticeable that Germany is below the European average - with the exception of the active substance group of polymyxins. (see graph)

Compared to the previous year, an increase in the area of HPCIA was recorded for fluoroquinolones by 0.4 t and macrolides by 4 t, and a decrease in polymyxins (with colistin) by 6 t. For the 3rd and 4th generation cephalosporins, consumption was reported to be unchanged from the previous year at 1.0 and 0.3 t respectively.

However, if one compares the 2011 consumptions with those of 2020, one can see a significant reduction in HPCIAs as well as in almost all antibiotic groups:[116]

114 https://www.bvl.bund.de/SharedDocs/Pressemitteilungen/05_tierarzneimittel/2021/2021_10_12_PI_Abgabemengen_Antibiotika_Tiermedizin.html

115 "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, pages 51-52 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf

116 ibid

Figures in tonnes	Fluoroquinolones	Macrolides	Polymyxins	Cephalosporins	Total antibiotics
2011	8,2	173	127	3,5	1706
2020	6,4	61	60	1,3	701

In Germany, the key figures on therapy frequency have been recorded since 2015 and published twice a year by the Federal Office of Consumer Protection and Food Safety. The therapy frequency results from the number of treatments by number of animals, corresponding to the treatments per animal. The data is published in the Federal Gazette every six months.

Calves for fattening (< 8 months), cattle for fattening (> 8 months), piglets (< 30 kg), pigs for fattening (> 30 kg), chickens for fattening and turkeys for fattening are recorded. In the event that the figures determined are exceeded on fattening farms, concepts for antibiotic minimisation are developed in cooperation with the veterinarian within the framework of a benchmarking system.[117]

It is important to note here that only fattening farms are covered by this system, while dairy cows, rearing calves, laying hens as well as sows and suckling piglets have so far been exempt from this reporting obligation.

In addition, the development of antibiotic use in livestock farming from 2013 to 2020 was determined within the framework of the so-called VetCAb Sentinel Study (Veterinary Consumption of Antibiotics).

In the pig farming sector in Germany, it can be observed that the proportion of farms that do not use antibiotics per half year is increasing.[118]

The size of the herd and the veterinarian in charge are important factors influencing the use of antibiotics.[119]

In the area of HPCIA, there was a decrease of 14.8 percent in the period 2013 to 2020. This is mainly due to the reduction in the use of polypeptide antibiotics.

In the area of cattle farming, the trend shows that larger farms have a significantly higher frequency of therapy than small farms[120]. Overall, however, antibiotic consumption in dairy and beef cattle farming is rather low compared to other animal species and countries.[121]

117 https://www.bmel.de/DE/themen/tiere/tierarzneimittel/entwicklung-kennzahlen-therapiehaeufigkeit.html

118 Schaekel F, May T, Seiler J, Hartmann M, Kreienbrock L (2017) Antibiotic drug usage in pigs in Germany - Are the class profiles changing? PLoS ONE 12(8): e0182661. https://doi.org/10.1371/journal.pone.0182661

119 Malin Hemme, Annemarie Käsbohrer, Christiane von Münchhausen, Maria Hartmann, Roswitha Merle, Lothar Kreienbrock. Differences in the calculation of farm-related antibiotic use in monitoring systems in Germany - a review. Berl Münch Tierärztl Wochenschr 130,(3,4) 2017 https://doi.org/10.2376/0005-9366-16065 https://www.vetline.de/unterschiede-in-der-berechnung-des-betriebsbezogenen-antibiotika-einsatzes-in-monitoringsystemen-in

120 Kasabova, Svetlana et al.: Development of antibiotic use in farm animal husbandry: results of the long-term scientific project "VetCAb-Sentinel" are available. Deutsches Tierärzteblatt 69, 8, (2021), pp. 920-925 https://www.bundestieraerztekammer.de/btk/dtbl/archiv/2021/artikel/DTBl_08_2021_VetCAb-Sentinel.pdf

121 Hommerich K, Ruddat I, Hartmann M, Werner N, Käsbohrer A and Kreienbrock L (2019) Monitoring Antibiotic Usage in German Dairy and Beef Cattle Farms-A Longitudinal Analysis. Front. Vet. Sci. 6:244. https://doi.org/10.3389/fvets.2019.00244

It would also make sense to introduce a benchmarking system in the dairy farming sector, as is already used in other countries.[122]

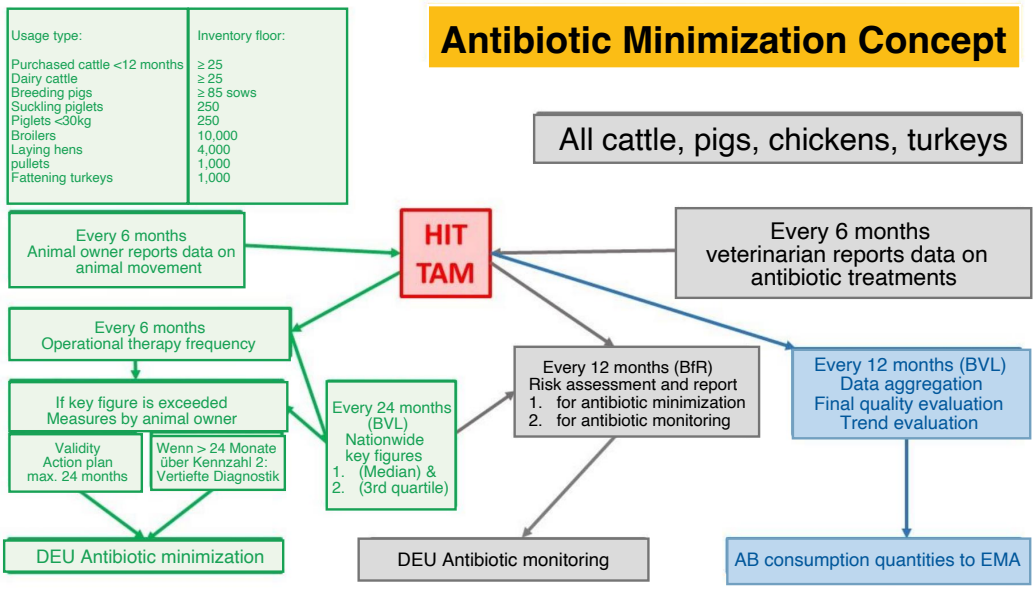
In dairy cow and rearing calf farms, the "vet" factor also plays a role. In dairy cows, the proportion of fluoroquinolones and cephalosporins is decreasing, while the proportion of beta-lactams and aminoglycosides is increasing.[123]

The authors of the VetCab-Sentinel study note that the key figure of treatment frequency can also lead to an over- or underestimation of the actual farm situation. Here, the information on the legally required veterinary dispensing and application receipts (AuA receipts) provide a more detailed overview of the number of animals, treatment duration and population.

According to the study, the figures relating to antibiotic use are only meaningful if animal species-specific quantification, allocation to specific active substances and multifactorial modelling of the data obtained are carried out.[124]

The medically relevant quantity, the dose per body weight in a treatment period (used daily dose UDD) as used by the institutions EMA, ECDC and EFSA, is not recorded in Germany, although it could be derived from the legally required AuA evidence.

[125]



According to the Federal Ministry of Food and Agriculture (BMEL), the antibiotic minimisation concept newly introduced with the 16th AMG amendment is to be redesigned. A discussion paper with key points has currently been prepared for this purpose.

122 ibid
123 ibid
124 Kasabova, Svetlana et al.: Development of antibiotic use in farm animal husbandry: results of the long-term scientific project "VetCAb-Sentinel" are available. Deutsches Tierärzteblatt 69, 8, (2021), pp. 920-925 https://www.bundestieraerztekammer.de/btk/dtbl/archiv/2021/artikel/DTBl_08_2021_VetCAb-Sentinel.pdf
125 BMEL Key points for a national antibiotic minimisation concept for animal husbandry (as of 07.01.2022) https://www.bmel.de/SharedDocs/Downloads/DE/_Tiere/Tiergesundheit/Tierarzneimittel/eckpunkte-nat-antibiotikaminimierung-tierhaltung.pdf?__blob=publicationFile&v=3

The paper provides, among other things, that in future the obligation to report antibiotic use lies with the veterinarian and no longer, as before, with the animal owner. Furthermore, far-reaching diagnostic measures - in particular antibiograms - are to be initiated if farms persistently exceed the index number 2. In addition, resistance genes, for example from isolated E. coli from faeces or from slaughterhouse samples from affected farms, should also be examined.

The veterinarian should receive feedback on his prescribing behaviour. The veterinarian is responsible for the selection of active substances and receives a proportional list of the active substances used, which are compared with the respective average values from the totality of veterinary prescriptions for the respective animal populations. Active substances of category A and B are marked separately.[126]

The Federal Association of Practising Veterinarians (bpt) is critical of some of the key points in the discussion paper. In addition to the indicator "therapy frequency", which in contrast to the DDD value does not allow for European comparability, the professional association also opposes "the intended possibility of comparing the prescribing behaviour of veterinarians". It is feared that practices, in order to stand out better in the ranking, will sort out farms that have problems in animal health as clientele and thus set the wrong incentives by the legislator.[127]

In Germany, a new Veterinary Medicinal Products Act (TAMG) came into force on 28 January 2022. It is to be applied together with EU Regulation 2019/6. It regulates at national level those contents of the new veterinary medicinal products law that are not directly applicable through Regulation 2019/6.

The TAMG is an independent new parent law. Previously, the regulations for veterinary medicine were listed in the Medicinal Products Act (AMG) alongside those for the human sector. With the new TAMG, the veterinary and human sectors are separated from each other and the provisions on veterinary medicinal products are deleted from the AMG.[128]

According to the wording of the law, veterinary medicinal products may now only be used in accordance with their marketing authorisation, i.e. in accordance with the manufacturer's instructions. A deviation from this is only possible in exceptional cases.[129]

Both the EU Regulation 2019/6 and the TAMG do not conclusively regulate all issues and contain a number of ordinance authorisations that open up possibilities for further specifications.

126 ibid

127 https://www.tieraerzteverband.de/bpt/berufspolitik/Positionen/arzneimittel-einsatz/dokumente/2022_01_31_Stellungnahme-zum-BMEL-Eckpunktepapier-Nationales-Antibiotikaminimierungskonzept-fuer-die-Tierhaltung.pdf

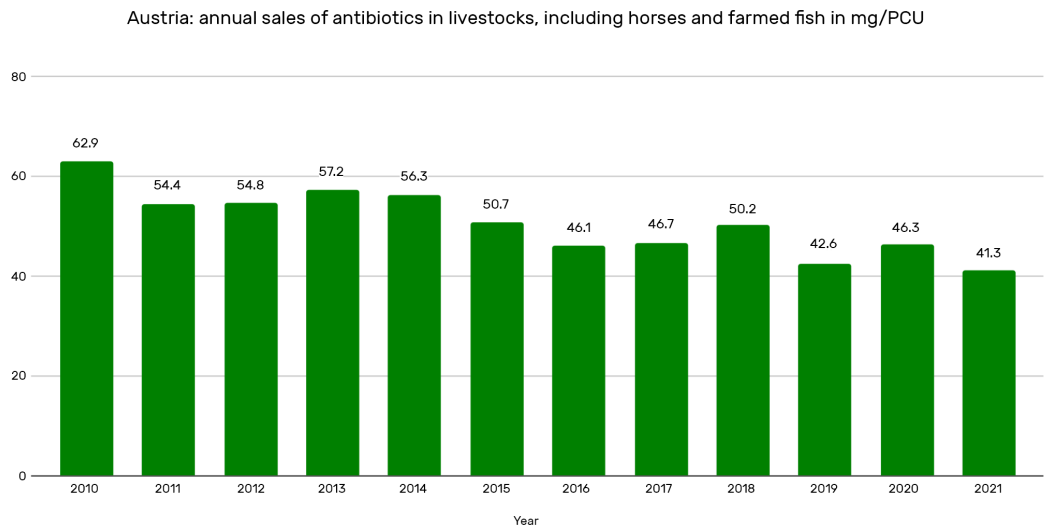
128 Gesetz zum Erlass eines Tierarzneimittelgesetzes und zur Anpassung arzneimittelrechtlicher und anderer Vorschriften vom 27. September 2021 https://www.bgbl.de/xaver/bgbl/start.xav?startbk=Bundesanzeiger_BGBl&start=//*[@attr_id=%27bgbl121s4530.pdf%27]#__bgbl__%2F%2F*%5B%40attr_id%3D%27bgbl121s4530.pdf%27%5D__1651820904617

129 Gesetz zum Erlass eines Tierarzneimittelgesetzes und zur Anpassung arzneimittelrechtlicher und anderer Vorschriften vom 27. September 2021 https://www.bgbl.de/xaver/bgbl/start.xav?startbk=Bundesanzeiger_BGBl&start=//*[@attr_id=%27bgbl121s4530.pdf%27]#__bgbl__%2F%2F*%5B%40attr_id%3D%27bgbl121s4530.pdf%27%5D__1651820904617

4.7. ANTIBIOTIC CONSUMPTION AND STRATEGY IN AUSTRIA

In a European comparison, the amount of antibiotics consumed per kg animal mass (PCU) in Austria is rather in the lower middle range with 46.3 mg/PCU and with 43.66 tonnes in absolute terms for food-producing animals in 2020[130]. However, there was an increase in consumption of 8.7% or 3.7 mg/PCU from 2019 to 2020.

In 2010, consumption in Austria was still 62.6 tonnes in total and 62.9 mg/PCU. Thus, a reduction of 30.3% in total and 26% in consumption by PCU could be achieved.[131]



Not only in total consumption but also in the area of the critical classes of active substances, the HPCIA, the country is consistently below the European average comparison values.

With regard to the individual groups of active ingredients, the tetracyclines continue to be in first place with 22.1 tonnes (50.7 percent). This is followed by the group of penicillins (7.4 tonnes or 16.8 percent), macrolides with 3.5 tonnes (8 percent) and sulphonamides (3.5 tonnes (8 percent).[132]

Sales volumes of Highest Priority Critically Important Antimicrobials (HPCIA) have fluctuated between 5.17 and 5.77 tonnes over the last five years, reaching 5.72 in 2020. Over the years, HPCIA maintain a relatively constant share of about 12% of the total.

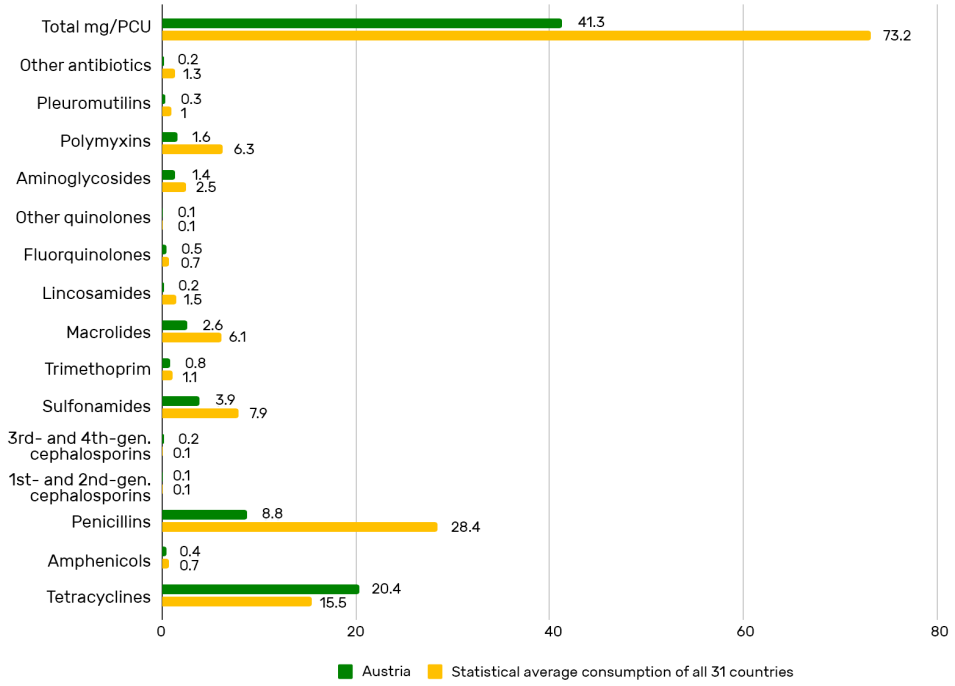
In the area of HPCIA, there has been a significant increase especially in macrolides from 2.91 tonnes in 2016 to 3.47 tonnes in 2020, while there were hardly any differences in the other groups.[133]

In a European comparison, Austria is a country with lower animal husbandry similar to Sweden. However, the consumption of antibiotics in Sweden is significantly lower, at about

130 https://esvacbi.ema.europa.eu/analytics/saw.dll?Dashboard
131 "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, pages 51-52 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf
132 ibid
133 Reinhard Fuchs, Univ.-Doz. DI Dr. Klemens Fuchs: Report on the distribution of antibiotics in veterinary medicine in Austria 2016-2020. AGES 15.10.2021

a quarter of the consumption in Austria. Different strategies in dealing with antibiotics are evident here.

Antibiotics sold in mg/PCU in 2020 compared: Austria compared to the average of 31 countries



In Austria, the distribution and consumption of antibiotics in veterinary medicine has been reported to AGES (Agentur für Ernährungssicherheit GmbH) since the introduction of the Veterinary Antibiotics Flow Regulation (BGBl. II No. 83/2014, amended BGBl. II No. 5/2016 and BGBl. II No. 127/2022). On the one hand, pharmaceutical companies are obliged to report their sales volumes to AGES annually, and on the other hand, veterinary home pharmacies are obliged to report their data on the dispensing of antibiotics in the respective previous year. The total quantities of active substances sold and dispensed are calculated from the reported sales and dispensing data. The active substances are divided into groups of active substances. Veterinarians who exclusively treat small animals have so far been exempt from the reporting obligation.

In Austria, a benchmarking system is used to provide feedback from the data collected to those veterinarians who participate in the volume flow survey.

The report sent ranks the consumption of the veterinarian in comparison to his colleagues and provides information on possible avoidance options in the use of antibiotics. As an indicator of antibiotic use, the quantities dispensed are converted into daily doses and standardised with the respective herd size (nDDDvet/year (defined daily dose for animals)). This shows the average number of days per year on which each animal on the farms in question was treated.

The pig farms also receive a farm report in which the dispensed quantity and active ingredient composition of the farm are listed and an antibiotic indicator is determined with the help of a farm categorisation. The antibiotic index results from the sum of the calculated daily doses per active ingredient (DDDvet) divided by the estimated total weight of pigs, determined from the stock, departure and slaughter reports of the farm in question.

This is put in relation to comparable farms in order to enable the farmer to classify his farm. The aim is to implement "best practice models" and to achieve a further reduction of antibiotics by identifying "high users".

An essential role in monitoring antibiotic use is played by the Austrian Animal Health Service (ÖTGD)[134], which is composed of the provincial animal health services and the Austrian Poultry Health Service (Österreichische Qualitätsgeflügelvereinigung, QGV)[135], coordinated by the Animal Health Service Austria Advisory Board established in October 2002.

The Animal Health Service Ordinance 2009[136] stipulates that the TGD is an institution for advising agricultural livestock farmers and for looking after livestock. One of the main objectives is to reduce the adverse effects of animal husbandry on livestock production so that the use of veterinary medicines can be minimised.

In addition, the cooperation "VET-Austria" between the Austrian Ministry of Consumer Protection (BMSGPK), the University of Veterinary Medicine Vienna and AGES has existed since 2013. The aim is the cooperative implementation of scientific work and research projects for which there is a common interest.[137]

For all animal species, the new EMA nomenclature was introduced for the individual antibiotic groups according to their relevance in human medicine.[138] Category A stands for "avoid", category B for "restrict", category C for "caution" and category D for "care". Category A antibiotics are not authorised as veterinary medicines in the EU. Category B antibiotics are of critical importance in human medicine and should only be used in exceptional cases.

Broken down into the individual animal species, it is noticeable that in each of the years 2016 to 2020, the largest amount of antibiotics sold or applied is used in pigs with 71.8% - 76.4%, followed by cattle with an average of 19.7% and poultry with an average of 6.2% of antibiotics. Thereby, in the last few years, a decrease could not be achieved in relation to the total quantity for any of the animal species examined (see figure).[139]

In their study, Firth et al (2022) emphasise the strikingly high antibiotic consumption in piglet rearing in Austria. The proportion of polymyxins, especially colistin, is also a cause for concern. This group of active substances belongs to the HPCIA. However, the number of piglet rearing farms in Austria is relatively small. This active ingredient is used in particular in the therapy of diseases of the gastrointestinal tract in connection with Escherichia coli (ETEC).

In all pig production areas, the majority of antimicrobial substances dispensed were in category D. Only piglet producers used a significant proportion of antimicrobial substances in category B. The majority of antimicrobial substances dispensed were in category B.[140] However, the

134 https://www.tgd.at
135 https://www.qgv.at
136 Ordinance of the Federal Minister for Health on the Recognition and Operation of Animal Health Services (Animal Health Service Ordinance 2009 - TGD-VO 2009) Federal Law Gazette II No. 434/2009 https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=20006592
137 Federal Ministry of Social Affairs, Health, Care and Consumer Protection (BMSGPK) National Action Plan on Antimicrobial Resistance NAP-AMR. Vienna, 2021 https://www.sozialministerium.at/dam/jcr:6f4dbf65-ff72-43dc-8db7-e3bfbee5440a/NAP-AMR.pdf
138 https://2020.fve.org/cms/wp-content/uploads/categorisation-antibiotics-use-animals-prudent-responsible-use_en.pdf
139 Ibidem
140 Reinhard Fuchs, Univ.-Doz. DI Dr. Klemens Fuchs: Report on the distribution of antibiotics in veterinary medicine in Austria 2016-2020. AGES 15.10.2021

differences in mass-based (mg/PCU) versus dose-based (DDDVET) evaluations became clear.[141]

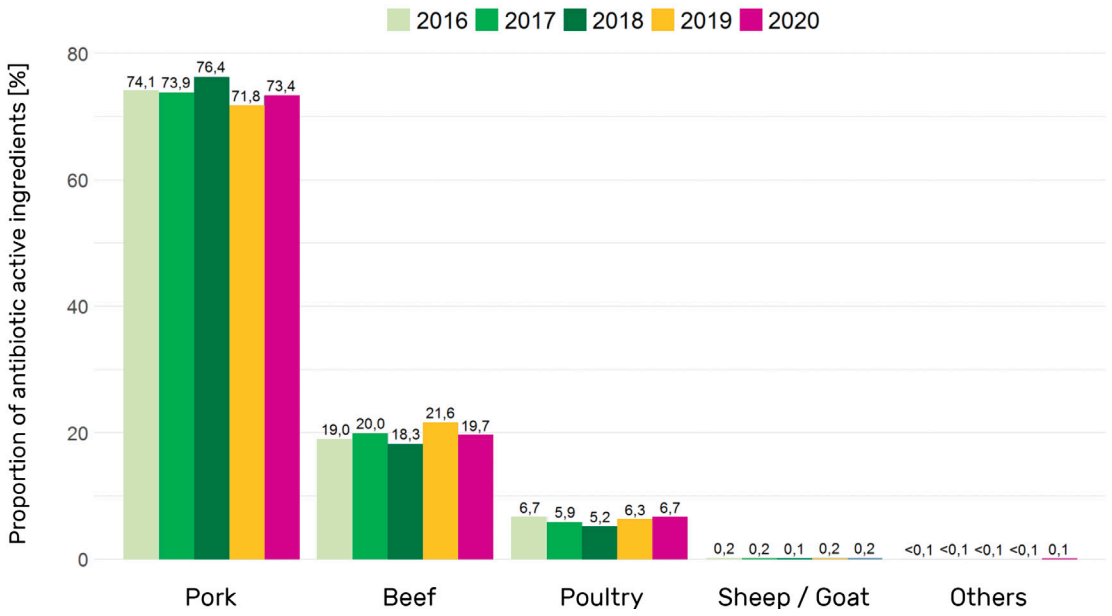


Fig: Proportion of the amount of animals sold per species, broken down by year

In dairy cattle farming, the greatest use of antibiotics is in the treatment of udder diseases and in the use of antibiotic dryers. In an international comparison, however, the use is relatively low, although the proportion of Highest Priority Critically Important Antimicrobials (HPCIA) is relatively high at 24.6 percent. More than two thirds of the HPCIA used in dairy cows are in the group of 3rd and 4th generation cephalosporins.

Due to their good efficacy and short waiting time, they are preferably used for udder diseases and used to treat udder infections.[142]

According to the Austrian Quality Poultry Association (QGV), there has been a significant decrease in the use of antibiotics in poultry farming between 2011 and 2020. The total amount of antibiotics used in 2011 was reduced from 4.71 tonnes to 2.36 tonnes in 2020. The majority of antibiotics used in poultry farming are for broilers (2020: 47 percent), followed by turkeys (2020 29 percent) and laying hens (2020 12 percent).[143]

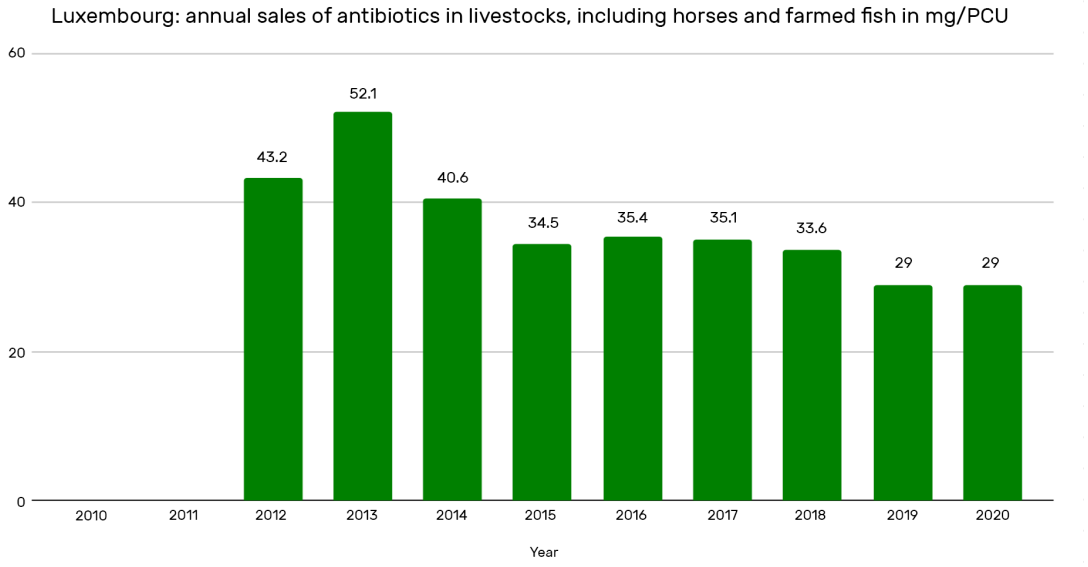
141 Firth, C.L.; Fuchs, R.; Fuchs,K. National Monitoring of Veterinary-Dispensed Antimicrobials for Use on Pig Farms in Austria:2015-2020. Antibiotics 2022, 11, 216. https://doi.org/10.3390/antibiotics11020216

142 Firth et al. (2017), Antimicrobial consumption on Austrian dairy farms: an observational study of udder disease treatments based on veterinary medication records. PeerJ 5:e4072; https://doi.org/10.7717/peerj.4072

143 QGV. Antibiotics Monitoring Report 2021 On the use of antibiotics in Austrian poultry farming. https://www.qgv.at/download/2130/

4.8. ANTIBIOTIC CONSUMPTION AND STRATEGY IN LUXEMBOURG

The first reports of antibiotics sold for use in veterinary medicine, which Luxembourg reported to ESVAC, date back to 2012. Except for an increase in 2013, the amount in mg/PCU decreased almost continuously from then on and has stagnated at the low level of 29 mg/PCU since 2019.[144]



In Luxembourg, the sale of antibiotics in veterinary medicine in 2020 was 29.0 mg/PCU, far below the average value of 89.0 mg/PCU of the countries reporting to ESVAC. For the 3rd and 4th generation cephalosporins, the value of 0.5 mg/PCU is also relatively low, but is above the average value of 0.2 mg/PCU by a factor of 2.5 for this group of antibiotic agents classified by the WHO as HPCIA. Only in Estonia was the value of 0.7 mg/PCU above that of Luxembourg, while the Czech Republic, Hungary and Slovakia were on a par with Luxembourg, also with 0.5 mg/PCU.

In 2017, a National Plan Antibiotics (NPA) or Plan National Antibiotiques (PNA) was developed for the years 2018 to 2022 in Luxembourg. The NPA is under the joint supervision of the Luxembourg Ministry of Health and the Ministry of Agriculture, Viticulture and Consumer Protection. The Ministry of the Environment was also involved in its development.[145]

The basic aim of the NPA is to reduce the occurrence, development and transmission of antibiotic resistance in Luxembourg in the livestock and human medicine sectors with a One Health approach.[146] Surveillance of antibiotic administration to pets does not take place in Luxembourg.[147] For pets, private laboratories offer antibiotic resistance testing. For farm animals, analyses are carried out by the National Laboratory of Veterinary Medicine. There

144 "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, pages 51-52 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf

145 "Plan National Antibiotiques 2018-2022", page 3+8 https://sante.public.lu/fr/publications/p/plan-national-antibiotiques-2018-2022.html

146 Ibidem page 8

147 Ibid page 13

is no national report on antibiotic resistance for pets and livestock. In Luxembourg, there is therefore no centralised surveillance system for recording antibiotic resistance in human and animal health. However, the number of isolates reported for the different types of bacteria is also low (due to the country, the author).[148]

Several strategy areas have been developed to achieve the set goals:

- For the area of official action: Establishment of a permanent steering mechanism[149]

- for the area of prevention, education and communication: Improve understanding of the problem of antibiotic resistance in the general population and among all medical and agricultural professionals involved through adapted communication and education[150] (For example, compulsory modules on the topic of antibiotic resistance are to be introduced at the national universities of applied sciences for health and agriculture.[151] In 2019, a flyer for livestock farmers was launched, in which criteria for the sensible use of antibiotics are defined and, above all, tips are given on how to avoid antibiotics and the benefits of vaccinations are also highlighted).[152]

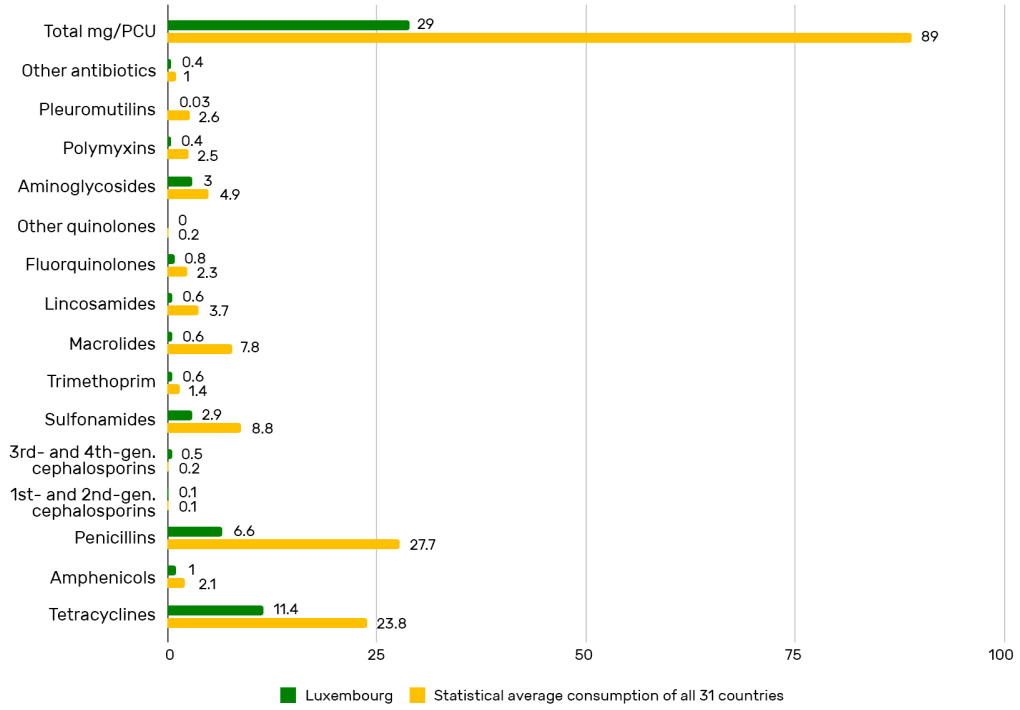
- for the area of treatment and diagnosis: promoting the good use of antibiotics in human and animal health (In the area of human health, the competent Scientific Council of Luxembourg has drawn up recommendations for the use of antibiotics for the treatment of the most common diseases in the outpatient setting. This also applies to antibiotic prophylaxis before surgical procedures. In the area of animal health, there are still no national recommendations for the treatment or correct use of antibiotics.[153] In the area of animal health, the topics of prevention and infection control through vaccination, biosecurity, hygiene, animal welfare and healthy nutrition are to be promoted in the future. From this, eligibility criteria for financial subsidies to livestock farmers are to be defined).[154]

- For the area of surveillance: Establishment of a national system for the surveillance of antibiotics (consumption of antibiotics, presence of antibiotics, antibiotic residues and resistant bacteria) and strengthening of the surveillance of HCAI[155] (The extent to which digital control of the use of antibiotics is to be introduced here and which exact criteria for use are to be recorded is not clear from the NPA).[156]

- For the area of research: development of a national research strategy on antibiotic resistance[157] (here, in a first step, the research needs on antibiotic resistance at international and national level are to be analysed, from which priorities for own research are to be derived together with all institutions involved).[158]

148 Ibidem page 14
149 Ibidem page 8
150 Ibidem page 8
151 Ibidem page 11
152 https://agriculture.public.lu/content/dam/agriculture/publications/ma/actualit%C3%A9s/antibiotikaresistenz-kampagne/MINSANTE-Flyer-100x210-2019-DE-HD.pdf
153 "Plan National Antibiotiques 2018-2022", page 12 https://sante.public.lu/fr/publications/p/plan-national-antibiotiques-2018-2022.html
154 Ibidem page 18
155 Ibidem page 8
156 The authors
157 Ibidem page 8
158 Ibidem page 25

Antibiotics sold in mg/PCU in 2020 in comparison: Luxembourg compared to the average of 31 countries



4.9. ANTIBIOTIC CONSUMPTION AND STRATEGY IN FRANCE

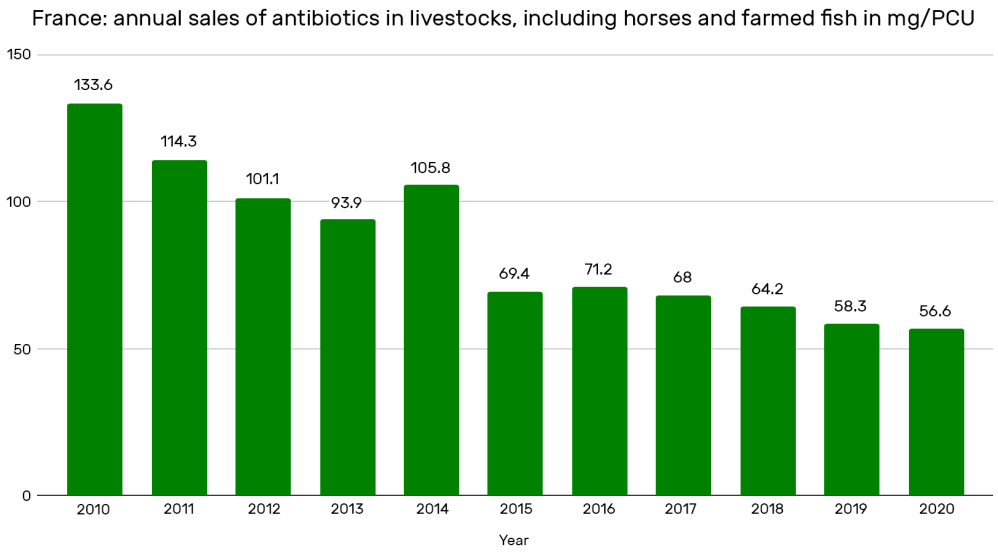
In France, domestic sales of antibiotics in veterinary medicine have been recorded by the Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES) since 1999. Since 2010, the French sales figures have been reported to ESVAC/EMA.

In 2010, France reported a sales value of 133.6 mg/PCU antibiotics, in 2020 it was 56.6 mg/PCU. The latter value is significantly below the ESVAC average value of 89.0 mg/PCU.[159]

The quantities of antibiotics sold are reported by the manufacturers of the preparations, include all official sales in France and are used to estimate for which animal species they were prescribed.[160]

159 "Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, pages 51-52 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf

160 https://www.anses.fr/en/content/monitoring-sales-veterinary-antimicrobials



In order to minimise the use of antibiotics in animal husbandry, a first "Ecoantibio Plan" was launched in France. It was valid from 2011 to 2016 and aimed to reduce the use of antibiotics in animal husbandry by 25%. During this period, a reduction of 36.5% was actually achieved. In 2014, the plan was supplemented. For 3rd and 4th generation fluoroquinolones cephalosporins, a reduction of 25% was to be achieved compared to the reference year 2013.

This reduction was also achieved and even exceeded. This was followed by the second Ecoantibio Plan for the years 2017 to 2021, which aimed to consolidate the achieved reduction in antibiotic use. The new plan includes communication and training measures, the use of alternatives to antimicrobials and improved prevention of animal diseases.

The second Ecoantibio plan also includes a specific target for colistin. This antimicrobial agent was to be reduced by 50% within five years in the cattle, pig and poultry sectors.[161] By 2020, a reduction of 66% was achieved. For cattle, the reduction was 48.1%, for pigs 74.8% and for poultry the use of colistin was reduced by 63.1%.[162]

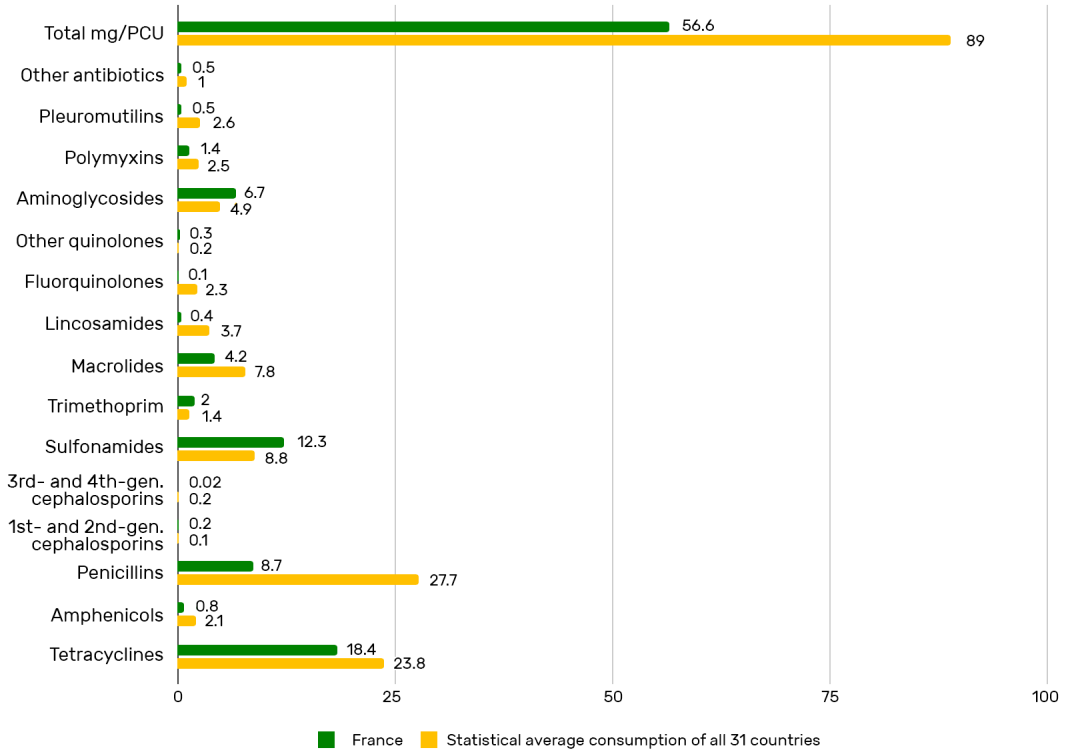
Compared to the average sales of the other reporting countries, France is almost consistently below the recorded average values. Only sulfonamides, aminoglycosides and trimethoprim exceed the average values.[163]

161 Anses. (2021). Suivi des ventes de médicaments vétérinaires contenant des antibiotiques en France en 2020, page 3-4 https://www.anses.fr/fr/system/files/ANMV-Ra-Antibiotiques2020.pdf

162 Ibidem page 40

163 Sales of veterinary antimicrobials agents in 31 European countries in 2019 and 2020"; Eleventh ESVAC report, 23 November 2021, page 29 https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf

Antibiotics sold in mg/PCU in 2020 in comparison: France compared to the average of 31 countries



Since the first Ecoantibio plan, several systems or bodies have been developed in France to allocate the antibiotic sales figures reported by the pharmaceutical industry to the different livestock holdings. These bodies involve different actors from farmers' associations, agricultural technical institutes as well as veterinarians, veterinary institutes, sectoral organisations of processors of animal products and Anses itself.

However, all these projects are based on voluntary measures by all stakeholders. Neither veterinary prescriptions nor actual applications are systemically recorded by animal species, age, disease or farm.

In order to meet future EU requirements under Regulation (EU) No 2021/578, France has yet to develop a specific IT system for the comprehensive collection of usage data. Such a system is to be developed under the project name "Calypso".[164]

For example, due to the lack of specific data, there is no yellow card system in France to encourage high users of antibiotics among livestock farmers to take measures to reduce their use.[165]

164 Anses. (2021). Suivi des ventes de médicaments vétérinaires contenant des antibiotiques en France en 2020, page 47-48 https://www.anses.fr/fr/system/files/ANMV-Ra-Antibiotiques2020.pdf
165 The authors

5. WAYS TO REDUCE AND/OR AVOID THE USE OF ANTIBIOTICS IN FARM ANIMALS

The analysis of different approaches in EU countries to reduce antibiotics in farm animals has made it clear that a combination of different measures brings significant success and that additional reductions are possible across the EU.

The fact that reduced antibiotic use produces less resistance has already been emphasised several times. However, the effect is also confirmed by a meta-study. The reduction in the risk of developing antibiotic resistance in animals with restricted antibiotic use was between 10 and 15% (total range 0-39), depending on the antibiotic group, the sample type and the bacteria being assessed. Whether this improves the resistance situation in humans is less clear. In particular, an improvement in the resistance situation could be determined in humans who had direct contact with food-producing animals.[166]

Basically, the following 3 areas can be identified that contribute to a reduction in antibiotic use:

1. Reduction of infections

    - More animal-related husbandry systems
    - Fewer animals in a confined space
    - Avoidance of infections through organisational and hygiene measures
    - Adapted feeding
    - Benchmarking systems

2. Preventive measures

    - Vaccinations
    - Use of pre- and probiotics and herbal substances

3. Responsible use of antibiotics

    - Compliance with antibiotic guidelines
    - Routinely no prophylaxis, few metaphylaxis
    - Dispense antibiotics only through veterinarians / more restrictive use
    - New therapeutic approaches

166 Tang et al. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis Lancet Planet Health 2017; 1: e316–27 http://dx.doi.org/10.1016/S2542-5196(17)30141-9

5.1. REDUCTION OF INFECTIONS

Healthy animals do not need to be treated with antibiotics. All measures that promote the health of food-producing animals thus contribute to a reduction of antibiotic-resistant bacteria in these animals and indirectly also in humans. Beyond the issue of antibiotic resistance, the measures proposed here generally have a positive effect on animal welfare.

Studies have shown a correlation between herd size and the use of antibiotics. Thus, it is mainly smaller farms that manage with a higher percentage without antibiotics in animal husbandry.[167]

As a basis, the rules for housing systems that enable a high level of animal welfare must be adhered to. These include:

- Safe, clean and animal-friendly housing
- Adequate space without overcrowding or with a reduced number of animals per area, reduction of stress through adapted housing systems and employment opportunities
- Good air quality through ventilation systems without draughts in the stalls
- Temperature and lighting adapted to animal species and age
- Manure management that reduces contamination of the animals with excreta and avoids contact with harmful gases
- All-in/all-out systems complete combined with hygiene measures
- Quarantine facilities for sick animals (pigs, cattle)[168]

All-in/all-out (AIAO) is a system in which mostly young animals are kept in fixed groups. The groups are usually at a similar level in terms of age, weight, production stage and condition. For example, the group stays together throughout the rearing phase and is also moved to new housing compartments together. When a group moves up, the previous pen compartment is completely emptied, cleaned and disinfected. This system has proven to be particularly effective in protecting the young animals from infections and stress.

Young animals (e.g. piglets, broilers, turkeys, young chickens and calves) with a developing specific immune system are particularly susceptible to diseases, therefore the use of antibiotics is highest in these animal groups.

167 Bericht des Bundesministeriums für Ernährung und Landwirtschaft über die Evaluierung des Antibiotikaminimierungskonzepts der 16. AMG-Novelle - Evaluierung auf Grund des § 58g des Arzneimittelgesetzes. https://www.bmel.de/SharedDocs/Downloads/DE/_Tiere/Tiergesundheit/Tierarzneimittel/16-AMG-Novelle-Bericht.pdf?__blob=publicationFile&v=2

168 Magnusson, U., Sternberg, S., Eklund, G., Rozstalnyy, A. 2019. Prudent and efficient use of antimicrobials in pigs and poultry. FAO Animal Production and Health Manual 23. Rome. FAO https://www.fao.org/3/ca6729en/ca6729en.pdf

Likewise, performance-oriented feeding prevents the occurrence of diseases. In addition to a sufficient supply of nutrients and adapted mineral content, feed and water must be of good quality. There are risks with regard to mycotoxins from e.g. Fusaria in grain as well as from e.g. moulds that develop during storage. Mycotoxins can negatively influence the immune system and thus promote the spread of infections. Waste from the food industry and other uncontrolled sources is a potential source of resistant infectious agents and should be banned as feed without thermal treatment. If antibiotics are administered via feed or drinkers, cleaning of troughs or water pipes must be ensured to avoid latent development of resistant germs through lowest doses of antibiotics in these areas.

External biosecurity refers to all measures that prevent the introduction of infectious diseases into an animal facility. This involves reducing all traffic around the facilities to a minimum. This includes a strict supply chain regarding the origin of delivered animals, i.e. only animals from one origin should ever be delivered to the subsequent housing system. Another entry point for germs are wild animals such as rodents or wild birds. Regular and effective pest control is essential.

This is complemented by internal biosecurity measures that prevent the spread of infections within a farm. Besides usual staff hygiene measures, these include all-in/all-out systems combined with cleaning and disinfection of the housing areas. Another measure is to only go from the youngest to the older animals when working in the housing systems to prevent spread to the most susceptible groups of animals.

In all biosecurity measures, compliance with the established rules and training of staff is crucial for the success of the measures.[169]

5.2. PREVENTIVE MEASURES

5.2.1. VACCINATIONS

Vaccination plays a key role in the prevention of infections and in the spread and severity of diseases, thus making a significant contribution to reducing antibiotic consumption. In order to achieve the widest possible acceptance of vaccination among veterinarians and farmers, vaccines must be available with high safety and efficacy, long-lasting protection and a user-friendly form of application.

New promising approaches include oral vaccines based on bacterial spores or vector-based vaccines.[170]

The majority of vaccines currently used in veterinary medicine are antiviral vaccines that can prevent secondary bacterial infections. Promising antibacterial vaccines include vaccines

169 Magnusson, U., Sternberg, S., Eklund, G., Rozstalnyy, A. 2019. Prudent and efficient use of antimicrobials in pigs and poultry. FAO Animal Production and Health Manual 23. Rome. FAO https://www.fao.org/3/ca6729en/ca6729en.pdf

170 Hoelzer et al. Vaccines as alternatives to antibiotics for food producing animals. Part 2: new approaches and potential solutions. Vet Res (2018) 49:70 https://doi.org/10.1186/s13567-018-0561-7

against Mycoplasma hyopneumoniae in pigs and against Salmonella spp. and Pasteurella in poultry.[171]

The following list contains infections for which new or further development of existing vaccines could lead to a significant reduction in antibiotic consumption:[172]

Pathogens: Diseases in chickens

- Escherichia coli: yolk sac infection, air sac inflammation, cellulitis
- Infectious bursal disease virus: Secondary bacterial infections
- Escherichia coli: Air pocket inflammation , cellulitis, salpingitis, peritonitis
- Clostridium perfringens, type A: Necrotic enteritis
- Coccidiosis: secondary bacterial infections
- Infectious bronchitis virus: Secondary bacterial infections

Pathogens: Diseases in pigs

- Streptococcus suis
- Haemophilus parasuis
- Pasteurella multocida: respiratory diseases
- Mycoplasma hyopneumoniae
- Actinobacillus pleuropneumoniae
- Porcine reproductive and respiratory syndrome virus: Secondary bacterial infections
- Swine influenza virus: Secondary bacterial infections
- Escherichia coli
- Lawsonia intracellularis
- Brachyspira spp (B. hyodysenteriae, B. pilosicoli)
- Rotavirus: Secondary bacterial infections

Within the framework of the long-term EU project SAPHIR (Strengthening Animal Production and Health through the Immune Response), research has been conducted since 2015 on new vaccines and strategies at the technological, immunological and socio-economic levels. The research focuses on pathogens that lead to major economic losses in livestock farming:

Beef	BRSV Mycoplasma bovis
Pig	PRSV Mycoplasma hyopneumoniae
Poultry	Eimeria spp Clostridium Perfringens

The results obtained are passed on to pharmaceutical companies for vaccine development.[173]

171 Kahn et al. From farm management to bacteriophage therapy: strategies to reduce antibiotic use in animal agriculture. Ann. N.Y. Acad. Sci. 1441 (2019) 31-39 https://doi.org/10.1111/nyas.14034
172 ibid
173 https://cordis.europa.eu/project/id/633184/results/de

With the help of modern antigen purification, it is possible to develop new active vaccines against multi-resistant bacteria such as Staph. aureus. At the same time, these methods can be used to produce effective monoclonal antibodies for the direct protection of patients.[174]

5.2.2. PROPHYLAXIS WITH PREBIOTICS, PROBIOTICS, ORGANIC ACIDS AND HERBAL ADDITIVES

Pre- and probiotics, essential oils and some herbal substances can promote gut health as feed additives. They support the development of a diverse microbiota in the gut of young animals. A good overview can be found in[175]

5.2.2.1. PREBIOTICS

Prebiotics are carbohydrates that are not digested by the body's own enzymes but provide a degradable substrate for the gut microbiota. Prebiotics specifically promote the composition of the microbiota by helping health-promoting bacteria (lactobacilli, bifidobacteria) to proliferate while repressing pathogenic bacteria such as E. coli or clostridia.

Prebiotics include numerous fibre substances consisting of oligosaccharides or fructo-oligosaccharides (FOS; oligofructose, fructans). They also include trans-galactooligosaccharides, glycooligosaccharides, maltooligosaccharides, xylooligosaccharides, yeast cell walls (mannan-oligosaccharides (MOS)) and gluco-oligosacharides.

For example, FOS supplementation may increase the thickness of the intestinal mucosa and the expression of certain cytokine genes in chickens. Changes in leukocyte composition and serum immunoglobulin levels suggest that FOS may be beneficial for gut health and immunity in broilers[176] . However, there are conflicting research results, so further research is needed.

5.2.2.2. PROBIOTICS

Probiotics are "living microorganisms" that promote health.[177] The term "probiotic" subsumes a variety of different microorganisms. These include bacteria, vegetative cells or spores, and yeasts. Even though it has been proven that probiotics have a positive influence on the health of farm animals, their mode of action is still the subject of current research.

174 Klimka, A., Mertins, S., Nicolai, A.K. et al. Epitope-specific immunity against Staphylococcus aureus coproporphyrinogen III oxidase. npj Vaccines 6, 11 (2021). https://doi.org/10.1038/s41541-020-00268-2

175 Muphy et al. EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA) EFSA Journal 2017;15(1):4666, 245 pp https://doi.org/10.2903/j.efsa.2017.4666

176 Shang Y, Regassa A, Kim JH and Kim WK, 2015. The effect of dietary fructooligosaccharide supplementation on growth performance, intestinal morphology, and immune responses in broiler chickens challenged with Salmonella Enteritidis lipopolysaccharides. Poultry Science, 94, 2887-2897. https://doi.org/10.3382/ps/pev275

177 Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ and Salminen S, 2014. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology and Hepatology, 11, 506-514. https://doi.org/10.1038/nrgastro.2014.66

The majority of studies on probiotics use strains of lactic acid bacteria (e.g. Lactobacillus spp. and Enterococcus spp.), Bifidobacteria, Bacillus spp. and Saccharomyces cerevisiae.

The results of the studies show:

- Improvement of growth performance
- Reduction of the prevalence and spread of zoonotic pathogens
- Reduction of infections in animals (e.g. necrotic enteritis in chickens or diarrhoea in pigs)
- Reduced mortality and improved animal welfare
- Immune modulation

Positive effects on diarrhoea in calves have been described several times. A meta-study with 15 randomised control trials confirms the effect that calves fed probiotics had significantly less diarrhoea than animals without the addition of probiotics.[178] Similar results are also found in pigs and gel fowl.

Probiotics in combination with prebiotics can stimulate the growth of the prebiotic microorganisms and thus improve the effect, this combination is called synbiotics. Here, too, a reduced tendency to diarrhoea, e.g. in piglets, has been observed in studies.[179]

5.2.2.3. ORGANIC ACIDS

Organic acids in feed also have a beneficial effect on animal performance. Various short-chain and medium-chain fatty acids are used, as well as other organic acids and their salts. The most commonly used are formic acid, acetic acid, lactic acid, propionic acid, butyric acid, sorbic acid, and benzoic acid.[180]

Some organic acids are more effective against acid-intolerant species such as E. coli, Salmonella spp. and Campylobacter spp. They improve the digestibility of nutrients and positively modify the microbiota composition.

In a review on the effects of the use of organic acids on the prevention of intestinal diseases, nutrient digestibility, immunity and performance of chickens and laying hens, the authors concluded that organic acids have a positive effect on poultry health and performance regardless of the type and levels used.[181]

178 Signorini M, Soto L, Zbrun M, Sequeira G, Rosmini M and Frizzo L, 2012. Impact of probiotic administration on the health and fecal microbiota of young calves: a meta-analysis of randomized controlled trials of lactic acid bacteria. Research in Veterinary Science, 93, 250-258. https://doi.org/10.1016/j.rvsc.2011.05.001

179 Krause DO, Bhandari SK, House JD and Nyachoti CM, 2010. Response of nursery pigs to a synbiotic preparation of starch and an anti-escherichia coli K88 probiotic. Applied and Environmental Microbiology, 76, 8192-8200. https://journals.asm.org/doi/10.1128/AEM.01427-10

180 Rasschaert G, Michiels J, Tagliabue M, Missotten J, De Smet S and Heyndrickx M, 2016. Effect of organic acids on Salmonella shedding and colonization in pigs on a farm with high Salmonella prevalence. Journal of Food Protection, 79, 51-58. https://doi.org/10.4315/0362-028X.JFP-15-183

181 Khan SH and Iqbal J, 2016. Recent advances in the role of organic acids in poultry nutrition. Journal of Applied Animal Research, 44, 359-369. https://doi.org/10.1080/09712119.2015.1079527

5.2.2.4. VEGETABLE ADDITIVES

Herbal feed additives have received much attention following the ban on antibiotic growth promoters in the European Union.

Although the term "phytobiotic" covers a wide range of substances of biological origin, these substances can be divided into four groups:

- Herbs (products of flowering, non-woody and non-permanent plants growing above ground)
- Plants (botanicals) (whole or processed parts of a plant, e.g. roots, leaves, bark)
- Essential oils (hydrodistilled extracts of volatile plant compounds)
- Oleoresins (extracts based on non-aqueous solvents)[182]

Reviews exist for pigs and poultry. Herbs and their extracts are used for their antioxidant and antimicrobial effects. However, it is crucial that studies include standardised ingredient analyses of the effective secondary plant compounds in order to compare effects.[183] [184]

Especially plants with immunomodulatory, antioxidant and anti-inflammatory potential are in focus for the prevention of bacterial infections, such as garlic, horseradish, cinnamon, pepper, thyme, oregano. Studies in piglets have shown good effects with garlic, horseradish and oregano.[185]

Cinnamaldehyde and eugenol are examples of plant substances that have effects on bacterial growth. Fermentation of plants can improve the promoting effect on animals and at the same time reduce antinutritive effects in the plants.

5.3. RATIONAL USE OF ANTIBIOTICS

The targeted use of antibiotics to treat infections can also be promoted through the detection of infectious agents or through appropriate individual diagnostics and resistance tests.

Therefore, there is a strategy at both European and many national levels to encourage veterinarians to carry out targeted testing before prescribing and administering antibiotics by issuing guidelines, legal requirements and recommendations.[186]

182 Windisch W and Kroismayr A, 2006. The effects of phytobiotics on performance and gut function in monogastrics. Proceedings of the World nutrition forum: The future of animal nutrition, 85-90.

183 Diarra MS and Malouin F, 2014. Antibiotics in Canadian poultry productions and anticipated alternatives. Frontiers in Microbiology, 5, 1-15. https://doi.org/10.3389/fmicb.2014.00282

184 De Lange C, Pluske J, Gong J and Nyachoti C, 2010. Strategic use of feed ingredients and feed additives to stimulate gut health and development in young pigs. Livestock Science, 134, 124-134. https://doi.org/10.1016/j.livsci.2010.06.117

185 Bilkei G, Bille G, Bilkei V and Bilkei M, 2011a. Influence of phytogenic feed additives on production and mortality of pigs - Part I: prophylactic effect of oregano in a pig fattening unit. Tierarztliche Umschau, 66, 157-162 - Bilkei G, Bille G, Bilkei V and Bilkei M, 2011b. Influence of phytogenic feed additives on production and mortality of pigs - Part II: effect of garlic (Allium sativum), horseradish (Aromatica rusticana) and doxycycline in prevention of postparturient diseases of the sows and pre- and postweaning mortality in piglets. Tierarztliche Umschau, 66, 253-257.

186 Briyne et al. Factors influencing antibiotic prescribing habits and use of sensitivity testing among veterinarians in Europe. Vet Rec,173, 19, 2013, 475-475. https://doi.org/10.1136/vr.101454

To decide on an antibiotic group, pathogen detection and an antibiogram after pathogen isolation are required. This also reduces the often ineffective use of antibiotics for viral infections. In practice, test systems are therefore necessary that enable a quick decision.

In a study in 25 European countries, it was determined which factors influence veterinarians in their decision for antibiotic therapy. According to the study, the main factors influencing antibiotic therapy and the choice of active ingredient are the results of sensitivity tests, the veterinarian's own experience and ease of use. The use of antibiograms varies greatly from country to country. In the survey, for example, these tests were carried out 15 times more frequently in Sweden than in Spain. Overall, antibiograms were used regularly in only 37.8% of cases.[187]

A higher acceptance of rapid tests can be achieved through reliable and quickly available results, easy handling or rapid test kits for direct application on site. Legal requirements or more education of farmers and veterinarians lead to higher test numbers.[188]

So far, rapid bacteriological tests have not been used sufficiently.

They are intended to answer the following questions:

- Is there a bacterial infection?
- Which bacteria are involved?
- Which resistances exist in the bacteria?
- Which antibiotics are most effective for treatment?[189]

Such tests make sense for the entire food chain to increase the safety of products of animal origin. Veterinary rapid bacteriological tests could best be used as an integrated element of a system to optimise antibiotic use in farm animals.

For example, live animals could only be sold with a certificate of vaccination in conjunction with a rapid bacterial test. This would also make it easier to identify weak points on individual farms. In addition, more information on antibiotic resistance would be available through widespread use.[190]

The basis for good veterinary practice in the treatment of bacterial infectious diseases is a scheme that serves as a guideline for all veterinarians. Here it is explicitly required: "A pathogen detection and an antibiogram after isolation of the pathogen are always necessary

- when changing an antibiotic
- in the course of therapy due to insufficient treatment success
- for regularly repeated or longer-term use in animal groups
- when combined antibiotics are administered for an indication
- in the event of a deviation from the conditions of approval (reclassification)"[191]

187 ibid
188 ibid
189 Bruce et al. Creating an innovation ecosystem for rapid diagnostic tests for livestock to support sustainable antibiotic use. Technology Analysis & Strategic Management 2021, 1-14 https://doi.org/10.1080/09537325.2021.1950678
190 ibid
191 Bundestierärztekammer (BTK) Guidelines for the careful handling of antibacterial veterinary medicinal products. Supplement to DTBl 3/2015 https://www.bundestieraerztekammer.de/tieraerzte/leitlinien/downloads/Antibiotika-Leitlinien_01-2015.pdf

Guidelines on the use of antibiotics in veterinary medicine can be found in almost all EU countries and can also be found in the EU "Guidelines for the prudent use of antimicrobials in veterinary medicine" (2015/C 299/04).[192]

From a legal point of view, the Veterinary Home Pharmacy Ordinance (TÄHAV § 12 c) also applies in Germany.[193] Following the antibiotic guidelines, it prescribes the use of an antibiogram

1. when changing the medicinal product with antibacterial effect in the course of treatment,
2. during treatment with a medicinal product with antibacterial effect,
   a) which occurs more frequently than once in certain age or production stages, or
   b) which exceeds the duration of seven days, unless a longer period for the duration of use was specified when the authorisation was granted, or in that case exceeds the longer period specified,
3. in the case of combined administration of medicinal products containing antibacterial agents for one indication, with the exception of authorised finished medicinal products containing a combination of antibacterial agents,
4. in case of deviation from the specifications of the marketing authorisation conditions of medicinal products with antibacterial agents or in case of treatment with medicinal products containing third- or fourth-generation cephalosporins or fluoroquinolones.[194]

A study on antibiotic minimisation in pig production shows that in several European countries, close cooperation between the farmer and the supervising veterinarian and the joint preparation of an antibiotic minimisation plan tailored to the respective farm has significant effects. In addition to improvements in water and feed management, improvements in husbandry and an adapted vaccination strategy are mentioned as possible building blocks. Another important aspect is the attempt to establish more individual animal treatments and thus a more targeted treatment of sick animals with antibiotics and thus to force a minimisation of feed-based group treatment.[195]

Consistent data collection and a derived benchmarking and monitoring system, as now introduced in many European countries (see e.g. the Netherlands, Denmark), give users feedback on their antibiotic use, lead to a sensitisation of farmers and also of veterinarians, and thus to a reduction in consumption quantities.[196]

192 Commission notice. Guidelines for the prudent use of antimicrobials in veterinary medicine (2015/C 299/04) https://health.ec.europa.eu/system/files/2016-11/2015_prudent_use_guidelines_en_0.pdf
193 Ordinance on Veterinary Home Pharmacies (TÄHAV) of 31.07.1975, last amended 21.2.2018 https://www.gesetze-im-internet.de/t_hav/
194 ibid
195 Raasch et al. Effectiveness of alternative measures to reduce antimicrobial usage in pig production in four European countriesPorcine Health Management (2020) 6:6, https://doi.org/10.1186/s40813-020-0145-6
196 Sanders et al. Monitoring of Farm-Level Antimicrobial Use to Guide Stewardship: Overview of Existing Systems and Analysis of Key Components and Processes. Front Vet Sci. 2020; 7: 540. https://doi.org/10.3389/fvets.2020.00540

5.4. NEW THERAPEUTIC APPROACHES

The German Antibiotic Resistance Strategy (DART) formulates in its objectives the promotion of research on the development of resistance and the development of alternative treatment methods.[197] The EMA (Committee for Medicinal Products for Veterinary Use, CVMP) and EFSA (Panel on Biological Hazards, BIOHAZ) are also compiling new approaches to combating AMR that could be incorporated into EU strategies.[198]

Zinc oxide (ZnO) is an authorised medicinal product in the EU used to prevent piglet diarrhoea. ZnO (1,000 to 3,000 mg/kg feed) reduces the incidence of intestinal disorders mainly after weaning and thus improves growth rates. This metal increases the absorption surface in the intestine and improves the intestinal barrier function. In addition, the non-specific immune system is activated.[199] [200]

Nanoparticles of silver or gold have been discussed in recent years as another possible treatment for multi-resistant microorganisms.[201] [202]

One promising approach is the use of bacteriophages. Bacteriophages are viruses that infect and kill certain bacteria and can thus be used specifically against certain pathogens. The development of resistance can be prevented, for example, by administering "phage cocktails" (consisting of 2 or more phages). Bacteriophages occur ubiquitously and have been the subject of research for some time.

Biotechnology companies have been rather cautious so far, as questions about the profitability and possible uses of bacteriophages as well as legal concerns about patent applications for living organisms are still unresolved. Although there is currently no approved product for use in livestock, phages are already being used successfully in the food industry, for example to combat Listeria monocytogenes in fish and meat products. Research is yielding promising results, especially in the control of important pathogens in poultry (Salmonella, E. coli, Campylobacter, Clostridium spp) and in pigs (Salmonella and E. coli). There are also first promising results with mastitis.[203]

Another alternative could be to disarm the bacteria, the so-called "antivirulence therapy". Here, targeted inhibition of virulence factors makes the bacteria less pathogenic. The

197 https://www.bundesgesundheitsministerium.de/themen/praevention/antibiotika-resistenzen/antibiotika-resistenzstrategie.html

198 Muphy et al. EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA) EFSA Journal 2017;15(1):4666, 245 pp https://doi.org/10.2903/j.efsa.2017.4666

199 Liu P, Pieper R, Rieger J, Vahjen W, Davin R, Plendl J, Meyer W and Zentek J, 2014. Effect of dietary zinc oxide on morphological characteristics, mucin composition and gene expression in the colon of weaned piglets. PloS One, 9, 1-10. https://doi.org/10.1371/journal.pone.0091091

200 Song ZH, Xiao K, Ke YL, Jiao LF and Hu CH, 2015. Zinc oxide influences mitogen-activated protein kinase and TGF-beta 1 signalling pathways, and enhances intestinal barrier integrity in weaned pigs. Innate Immunity, 21, 341-348. https://doi.org/10.1177/1753425914536450

201 Mapara N, Sharma M, Shriram V, Bharadwaj R, Mohite K and Kumar V, 2015. Antimicrobial potentials of Helicteres isora silver nanoparticles against extensively drug-resistant (XDR) clinical isolates of Pseudomonas aeruginosa. Applied Microbiology and Biotechnology, 99, 10655-10667. https://doi.org/10.1007/s00253-015-6938-x

202 Kaur K, Reddy S, Barathe P, Shriram V, Anand U, Procków J and Kumar V (2021) Combating Drug-Resistant Bacteria Using Photothermally Active Nanomaterials: A Perspective Review. Front. Microbiol. 12:747019. https://doi.org/10.3389/fmicb.2021.747019

203 Kahn et al. From farm management to bacteriophage therapy: strategies to reduce antibiotic use in animal agriculture. Ann. N.Y. Acad. Sci. 1441 (2019) 31-39 https://doi.org/10.1111/nyas.14034

inhibition of toxins or adhesins of a pathogen could possibly weaken or prevent an infection in such a way that treatment with antibiotics is no longer necessary. This approach seems particularly promising for germs in which a single virulence factor is responsible for triggering a disease.[204]

Preventing biofilm formation is another target of novel substances. The disruption of bacterial communication, so-called "quorum sensing", also prevents the spread of resistance. Thus, processes that lead to the virulence or pathogenicity of certain pathogens are also prevented by disrupting these communication pathways. This more promising approach is quorum quenching (QQ), which refers to processes by which this language can be disrupted and interrupted. Molecules and enzymes that interrupt this language could be the antibiotics of the future.[205] [206] [207]

The goal for the future must be to specifically link these different approaches for the individual animal species, age groups and types of use and to use them in practice. In a statement from 2013, the Leopoldina recommends that, on the one hand, research efforts must be intensified, especially genome research on the emergence and spread of resistance genes. On the other hand, it recommends adapting the framework conditions in such a way that it is easier to effectively implement scientific findings in practice.[208]

5.5. BREEDING ASPECTS USING THE EXAMPLE OF POULTRY

When breeding pets, animals such as cats and dogs are selected for traits that are useful to humans. Such traits can be good looks, adaptability to humans, protective behaviour towards humans and many other traits that seem beneficial to the respective owners of the animals.

In contrast to domestic animals, the breeding of farm animals focuses on their economic performance. Laying hens, for example, should lay as many eggs as possible in as short a time as possible and consume as little feed as possible. In order to bring out such positive characteristics from the point of view of the livestock owner, farm animal husbandry of pigs and poultry now almost exclusively uses hybrids. Hybrids are crosses of animal breeds that are genetically as far apart as possible, but which can still produce offspring together. These hybrid offspring are almost always much more efficient than their parents. The hybrids most people are familiar with are probably the mule and the hinny. The mule is a cross between a domestic horse mare and a domestic donkey stallion, the hinny is a cross between a domestic

204 Leopoldina report, BR report https://www.br.de/wissen/antibiotika-multiresistente-keime-forschung-bakteriophagen-antivirulenz-therapien-100.htm

205 Zhao W, Lorenz N, Jung K, Sieber SA. Fimbrolide Natural Products Disrupt Bioluminescence of Vibrio By Targeting Autoinducer Biosynthesis and Luciferase Activity Angew Chem Int Ed Engl. 2016 Jan 18;55(3):1187-91 https://doi.org/10.1002/anie.201508052

206 Weiland-Bräuer, N., Schmitz-Streit, R.A. Quorum quenching-disrupting peace between bacterial relationships. Biospektrum 22, 362-364 (2016). https://doi.org/10.1007/s12268-016-0698-8

207 Vollstedt, C., & Streit, W. (2021). Quorum quenching: speech disorders in the microbial world. Biology in Our Time, 51(2), 142-149. https://doi.org/10.11576/biuz-4250

208 Antibiotics Research: Problems and Perspectives - Statement. Academy of Sciences in Hamburg / German Academy of Sciences Leopoldina - National Academy of Sciences. De Gruyter 2013 ISBN 978-3-11-030667-5 https://www.leopoldina.org/uploads/tx_leopublication/2012_11_9_Antibiotika_Buch_01.pdf

horse stallion and a domestic donkey mare. Especially the mule combines the positive performance characteristics of horses with the endurance and insensitivity of donkeys. This is why mules are mainly used as draught and pack animals. Like most hybrids, however, mules are, with rare exceptions, no longer able to reproduce.

In the breeding of laying hen hybrids, offspring are produced from four different lines, the so-called pure breed. The parents of the purebreds A, B, C and D are genetically very closely related through inbreeding. The now produced grandparents A and B are crossed with each other again. The same applies to animals C and D. The parents with the genetic traits AB and CD are crossed again and thus the final product, the laying hen with the traits of ABCD, is created. A hen produced in this way lays an egg almost every day in the complete absence of roosters. However, the eggs are also no longer incubable and not suitable for breeding offspring. When the laying performance of such a hybrid hen begins to decline after a good year, the laying hens are removed and slaughtered and new animals are purchased from the breeding farm. It is not possible for livestock farmers to breed their own hens.

Of course, laying hen hybrids should also be healthy and not become sick under the conditions set by humans, because diseases in turn have a negative impact on the number of eggs laid or can lead to the death of the animals. However, in order to combat any diseases that may occur, there are now also numerous veterinary preparations available to livestock farmers. Almost all of these were originally developed to combat human diseases, but they work in vertebrates with the same mechanisms as in humans. In the past, breeding goals such as toughness and robustness in laying hybrids have almost always led to losses in the economic parameters that are important for farmers, such as laying performance and feed conversion. Because of the veterinary medicine available at the same time, characteristics such as a particularly strong endogenous defence against microbes do not play a significant role in the breeding of laying hens.[209]

In breeding trials at Wageningen University in the Netherlands, which ended with a PhD in 2018, it was possible to achieve significantly better disease resistance in laying hen hybrids without reducing the economic performance characteristics of the animals. At the same time, the new selection parameter should be easy and cheap to measure.[210]

The researchers' breeding relied on an increase in natural antibodies (NAb) in the animals' serum. Natural antibodies are the immune system's first response to pathogens. In contrast to antibodies developed by disease-specific vaccines, NAbs only give a non-specific response to the invaded pathogen, so they cannot fight it as specifically, but are often nevertheless successful.

It was already known to the researchers at the time of the breeding experiments that certain antibodies positively influence the general life expectancy of the laying hens and that their expression in animals can probably be passed on hereditarily. These antibodies have a special binding ability to the protein KHL (Keyhole Limpet Hemocyanin), which is available in biological research and is extracted from the Great California Keyhole Snail.

209 The authors
210 Selective breeding on natural Antibodies in Chickens, Tom V. L. Berghof, Wageningen, 19 January 2018, page 8-11 https://library.wur.nl/WebQuery/wurpubs/fulltext/426278

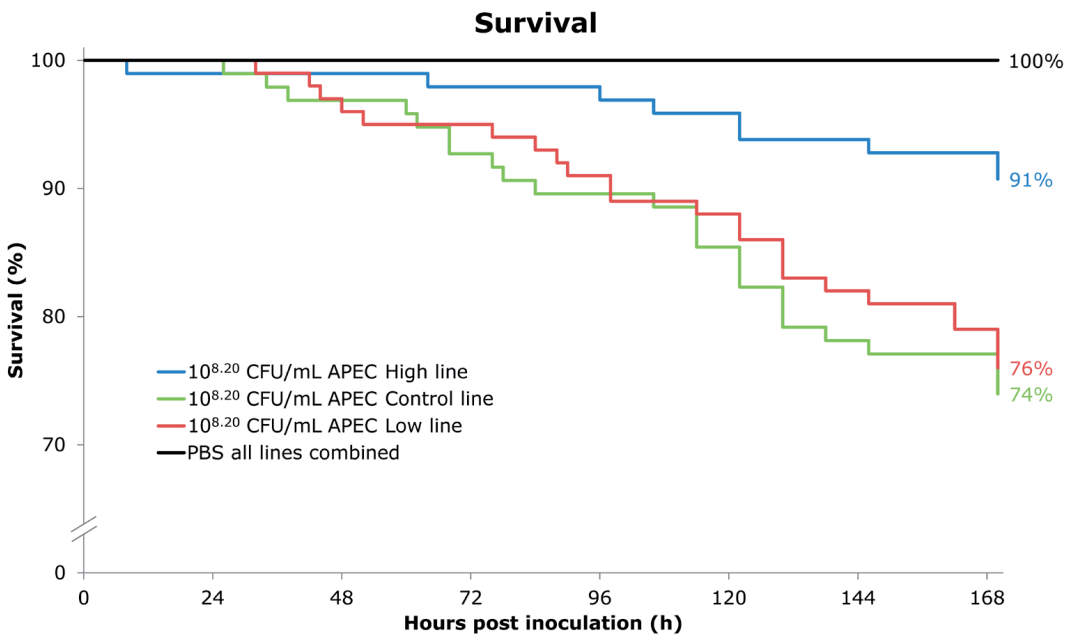
From an initial population of 3,700 male and female laying hybrids, those hens and cocks were selected for NAbs over six generations. At 16 weeks of age, the titer in the plasma of the animals was measured for NAbs with KHL binding ability in all generations. The animals were then divided into a line of animals with NAbs with high KHL binding ability, a line with low KHL binding ability and a non-selected control line and bred over six generations. Each generation consisted of about 600 animals per line.[211]

In two experiments, 100 animals from each of the different groups were artificially infected with the bacterium Avian Pathogenic Escheria coli (APEC) in the fourth and sixth generation.[212]

APEC causes colibacillosis in poultry, a disease that is associated with high morbidity and mortality and causes significant economic losses in the poultry industry worldwide.[213]

After the artificially induced infection, the animals were examined for their health status over a period of seven days. In the first experiment in particular, there were significant differences between the animals with a high presence of NAbs and the animals from the control line and those with low NAbs. In the second experiment, the differences were then no longer so clear. The researchers suspect the reason for this to be a lower dose of APEC with which the animals were infected. Taken together over both experiments, however, the mortality of the animals selected for NAbs still fell by 50 to 60 percent.[214]

[215]



The laying performance of the laying hens selected for natural antibodies was the same as that of the control line. Whether the results of the research will find their way into the further selection of disease-resistant laying hybrids is not known at this time.[216]

211 Ibidem page 8, 9 and 86
212 Ibidem page 110-112
213 https://refubium.fu-berlin.de/handle/fub188/2623
214 Selective breeding on natural Antibodies in Chickens, Tom V. L. Berghof, Wageningen, 19 January 2018, pp. 110-112 https://library.wur.nl/WebQuery/wurpubs/fulltext/426278
215 Ibidem page 119
216 Email from Tom Berghof from 12.05.2022

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