3

INTRODUCTION TO DANMAP

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3.1 Background

DANMAP – the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme was established in 1995 to predict and counteract the emergence of antimicrobial resistance in both animals and humans in Denmark. In the 90s, many European countries were focusing on probable and possible relationships between antimicrobial use (AMU) and the development of antimicrobial resistance (AMR). The Danish initiative thus coincided with an overall strive to reduce or prohibit the use of animal growth promoters in the European Union and was paralleled by the introduction of similar programmes of surveillance in other northern and middle European countries within the decade.

The focus was on producing evidence for the linkage between AMU and AMR, point out possible knowledge gaps and establish monitoring systems that would create data for action. Connected research today focuses on evolution of bacteria and their survival mechanisms and resistance traits. Simultaneously, research in mechanisms of spread has gained increasing interest as has improvement of diagnostic methods.

The key objectives of DANMAP are:

- To establish the "state of the nation" on to the use of antimicrobial agents in food animals and humans
- To collect and collate available national data on 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. in transmission of resistance or possible associations between antimicrobial consumption and antimicrobial resistance
- To ensure data availability for veterinarians, medical doctors and other health professionals for the development of antibiotic guidelines for treatment
- To act as a knowledge base for authorities and politicians when performing risk assessment and management, thus supporting decision making in the prevention and control of resistant bacterial infections

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The risk of AMR

Bacteria can be inherent resistant or become resistant either by spontaneous mutation or by transfer of resistance genes from other bacteria. Resistant strains are favoured, when use of antimicrobial agents provide a selective pressure. This occurs in humans as well as in animals undergoing antimicrobial treatment. Resistant bacteria can spread between humans in the community, at healthcare centres and at hospitals. Furthermore, resistant bacteria from animals can be transmitted to humans either through direct contact with animals and their environment or through ingestion of contaminated food or other contaminated vehicles.

Antimicrobial treatment failure may occur if the ingested resistant bacteria are a direct cause of disease, or if resistance determinants are transferred to pathogenic bacteria causing the disease. Bacteria may be resistant to several – sometimes all – antimicrobial agents available for treatment, increasing the risk of treatment failure.

Currently there is only a limited number of antimicrobial agents, with novel modes of actions, under development by the pharmaceutical industry. Therefore, it is vital for public health organisations to ensure the continued effectiveness of compounds considered critically important to human treatment by ensuring prudent use for both humans and animals.

Prudent use should include considerations on possible restrictions of critical antimicrobial agents, so these can be reserved for use in humans primarily, to consider the introduction of new compounds for use in one sector only, as well as to eliminate all overuse. Only humans and animals suffering from an infection responsive to antimicrobial treatment should be exposed to antimicrobial agents.

The DANMAP surveillance system

DANMAP surveillance relies on four equally important components: well-established and well-functioning diagnostic systems, well-designed and representative surveys, reliable registers as well as mutual trust and openness between all collaborators.

The monitoring programme was initially developed using a bottom-up approach by researchers based on frequent disussions and exchange of knowledge and results from research. Since then, DANMAP has evolved into a governmentally supported organisation. However, much of the design of the programme, including participation of the human laboratories and referral of strains is still based on a voluntary principle.

A positive side effect of the regular meetings and exchange between stakeholders is that these prove helpful in other aspects, for example, by contributing to a common knowledge pool regarding laboratory methods This ensures and contributes to continuous improvements and harmonisation of much of the laboratory work. Meetings across sectors and between different stakeholders also contribute to a better mutual understanding, facilitating development of the current system and increasing the willingness to listen to each other and work towards mutual goals.

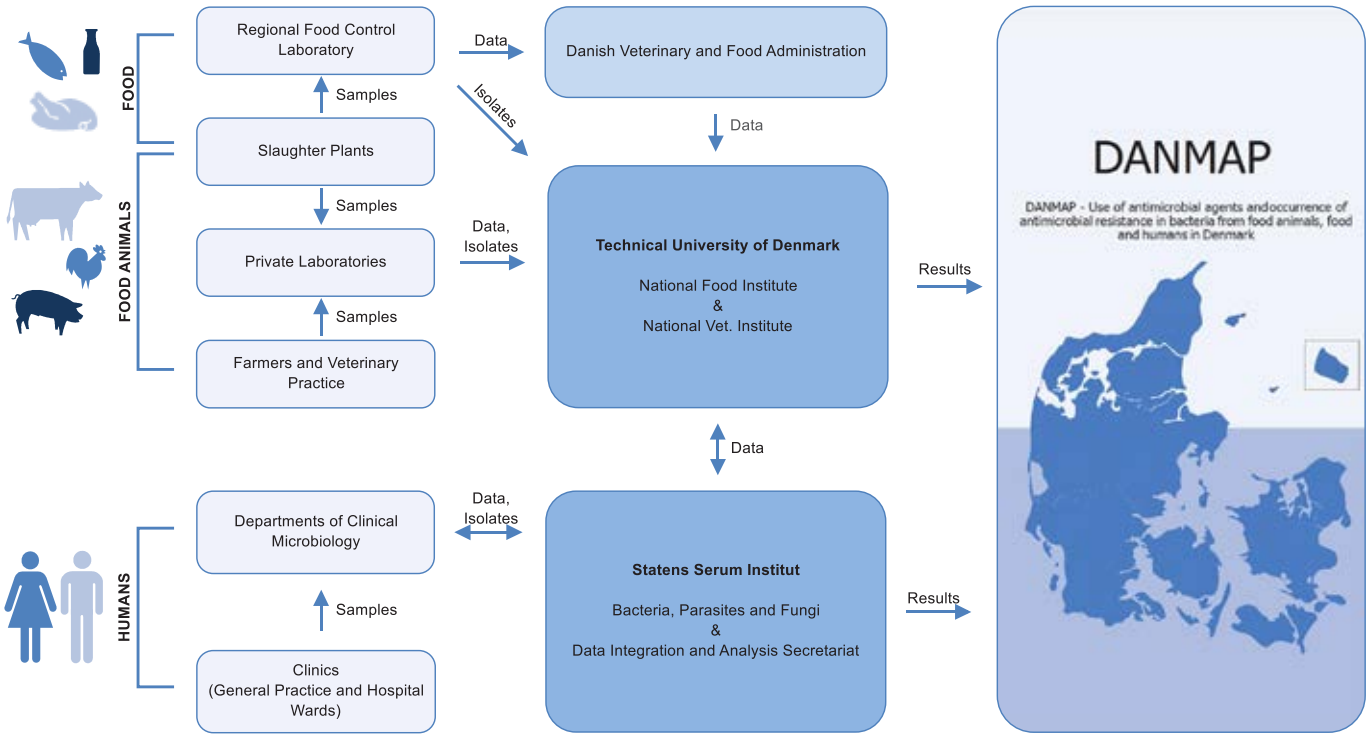
DANMAP today is a governmentally supported programme with objectives, roles and tasks. While participation from several stakeholders continues to be voluntary, DANMAP is primarily financed by the two ministries. Support from the ministries has also helped building the databases and ensuring the registers, which the current surveillance system relies upon. The system builds on transparency, mutual agreements and a standardised approach, which ensures consistency and continuity. For further information, please read chapter 2, "DANMAP – A 20 year perspective" in DANMAP 2015.

Surveillance is a complex undertaking and DANMAP encompasses many different surveillance components and covers resistance in different populations and contexts. Three categories of bacteria are always included in DANMAP:

- Human clinical isolates to reflect the antimicrobial resistance levels in the human population that seek medical care.
- Food borne zoonotic bacteria along the whole farm-to-patient chain to monitor the levels of antimicrobial resistance in shared pathogens
- Indicator bacteria, enterococci and *E. coli*, from healthy food-producing animals to monitor status of antimicrobial resistance in the animal reservoirs.

Since 1995, a main purpose of DANMAP has been to surveil the entire chain from farm to fork to sickbed. The organisation and collection of DANMAP resistance data is presented in Figure 3.1. The diagram shows the interdisciplinary collaboration between sectors and organisations.

Figure 3.1 Organisation of the DANMAP collaboration regarding resistance data and data flow DANMAP 2018



For surveillance purposes and in outbreak situations the recent introduction of whole genome sequencing (WGS) has been a big step forward. In the clinical situation, the phenotypical testing may still be highly relevant, more feasible, cheaper and sometimes faster. Phenotypical testing is also extensively used in combination with WGS to describe and determine which resistance genes are relevant to look for when using molecular analyses.

Bacterial isolates from food, food animals and humans are submitted to Statens Serum Institut, the Regional Food Control Laboratory or the Technical University of Denmark for further phenotypic and genotypic characterisation (Figure 3.1). In 2018, WGS is performed on selected, single isolates. These isolates are analysed for clonal relationship, as well as antimicrobial resistance genotypes (including ESBL and AmpC genes), and the presence of mobile elements such as plasmids. The outcomes are used for surveillance as well as detection of outbreaks. Furthermore, when specific clones carrying the same antimicrobial resistance genes and plasmids are found among both food and human isolates, genomic data analysis such as core genome multilocus sequence typing (cgMLST) and single nucleotide polymorphism (SNP) calling, are used to examine possible transmission between the reservoirs. The choice of the varying methods in surveilling different bacteria and infections is described in more detail in the different chapters and sections of the report.

3.2 Information on demographics, food production and data flow

The following sections present some general information about the human population in Denmark in 2018, the production of food animals and meat. It also provides an overview of the antimicrobial agents for systemic and intramammary therapeutic use in humans and animals in 2018.

3.2.1 Populations and productions

Human population and healthcare system

During the past two decades, the human population in Denmark has increased from approximately 5.2 million inhabitants in 1995 to approximately 5.8 million in 2018 (www.dst.dk). Simultaneously, the average age increased (Figure 3.2). In 2018, the national average age was 41.5 years. The population, which could potentially have received antimicrobial treatment in 2018, is shown as regional distribution in Figure 3.3.
In Denmark, microbiological analyses are carried out by altogether ten departments of clinical microbiolgy (DCMs), situated at the main regional hospitals in Denmark, also presented in Figure 3.3. Analyses cover all samples from public hospitals and most samples from general practitioners (GPs). In addition, some GPs perform culturing of urinary samples from their patients. In the Capitol region one private laboratory also performs analyses for the GPs.

Figure 3.2 Changes in regional distribution of average age, Denmark DANMAP 2018

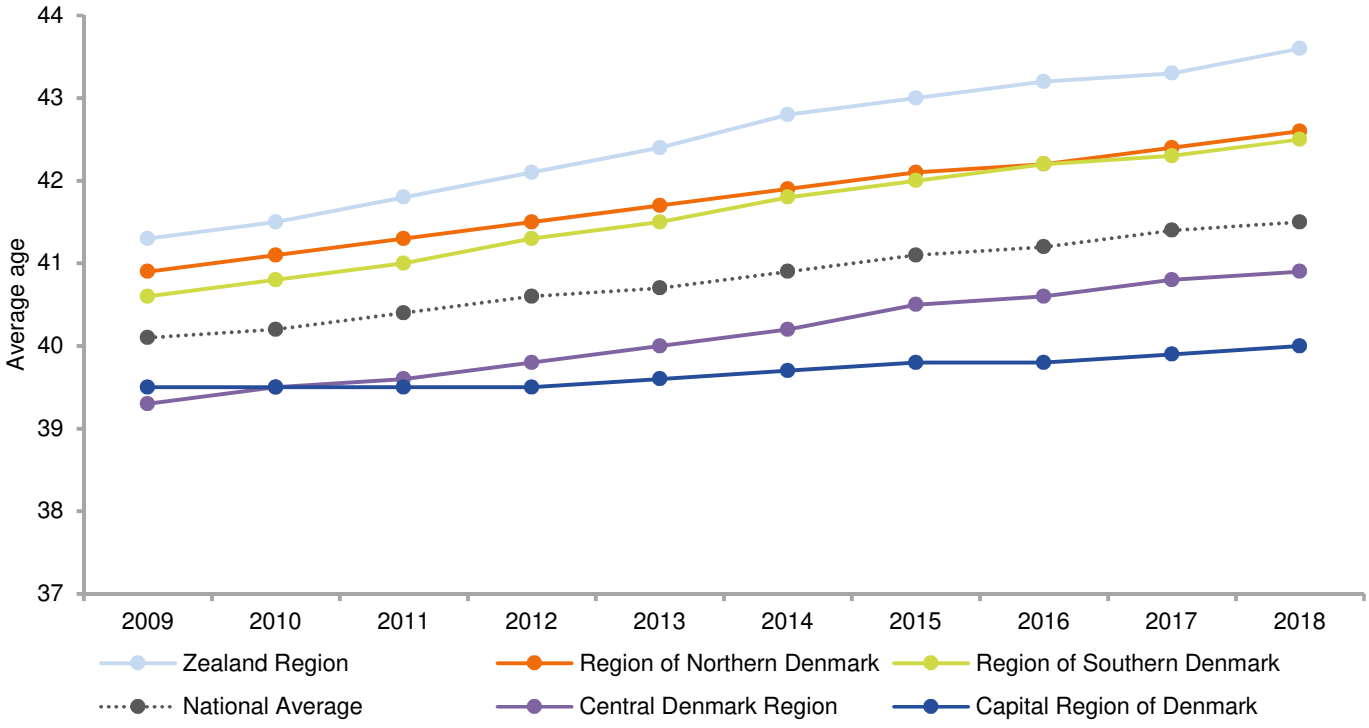
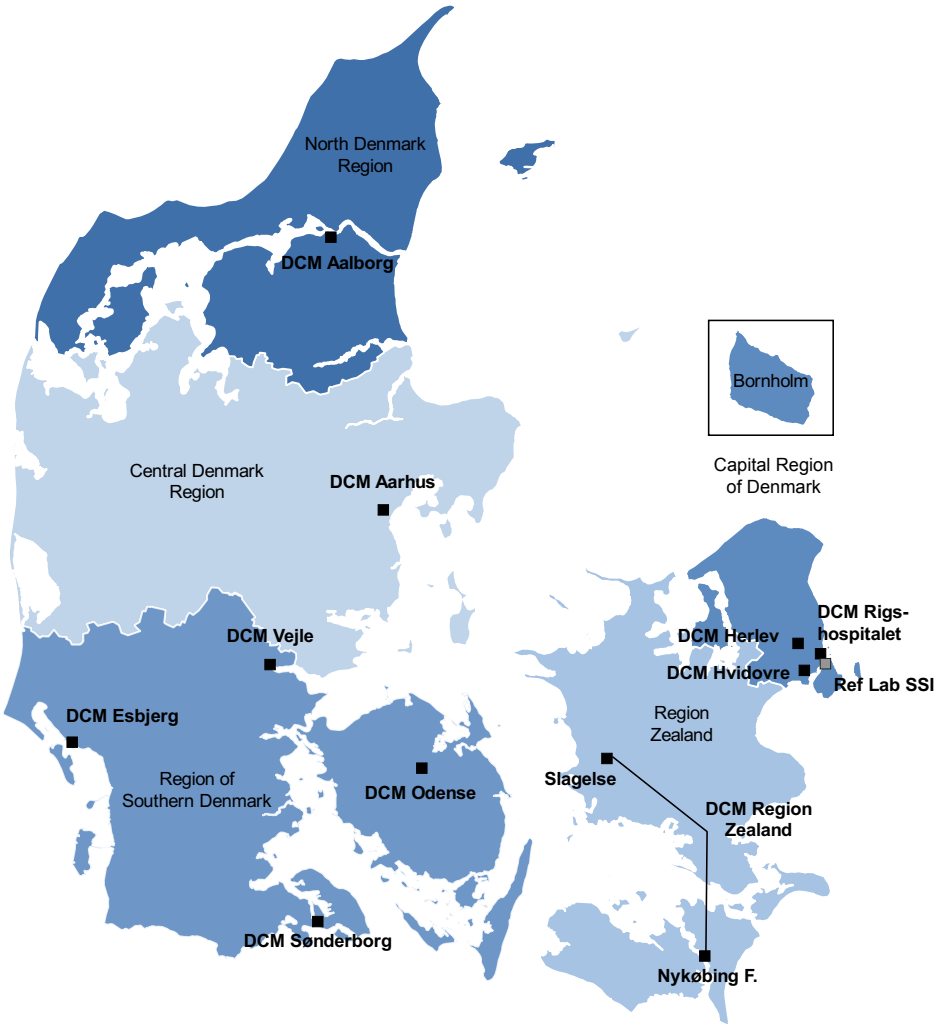


Figure 3.3 The five Danish healthcare regions and their respective population distributions. In addition, the ten DCM are marked by black squares. The grey square indicates the reference laboratory situated at SSI DANMAP 2018



North Denmark Region

No. of inhabitants	589,148
No. of inhabitants/km²	74
No. of inhabitants/GP	1,957

Central Denmark Region

No. of inhabitants	1,313,596
No. of inhabitants/km²	101
No. of inhabitants/GP	1,628

Capital Region of Denmark

No. of inhabitants	1,822,659
No. of inhabitants/km²	712
No. of inhabitants/GP	1,733

Region Zealand

No. of inhabitants	835,024
No. of inhabitants/km²	115
No. of inhabitants/GP	1,815

Region of Southern Denmark

No. of inhabitants	1,220,763
No. of inhabitants/km²	100
No. of inhabitants/GP	1,561

GP = general practitioner.

Source: Statistics Denmark (www.dst.dk) and the Danish Medical Association (www.laeger.dk)

Animal population and food production system

Denmark is an agricultural country, with more than half of its area managed by the agricultural sector. The agricultural sector contributes to employment with around 146,000 jobs in the primary production and processing, and contributes around 25% of the Danish export earnings. Livestock is of great importance and approximately 25% of the agricultural enterprises are specialised in the production of livestock, mainly pigs, cattle, chicken and mink [Danish Agriculture and Food Council, 2017].

The production of food animals and the production of meat and milk are presented in Table 3.1 and 3.2. In 2018, the number of pigs produced increased by approximately 3% compared to 2017, and the number of exported fattening pigs (15-50 kg) continued to increase by approximately 6%. Since 2004, the total exports of fattening pigs have increased more than seven-fold [Statistics Denmark, Danish Agriculture and Food Council, 2017].

From 2017 to 2018, the cattle production experienced a slight increase in general, the number of cattle slaughtered increased by approximately 5%, the number of dairy remained approximately the same level, while the amount of milk produced increased by approximately 2,5% [Statistics Denmark].

The number of broilers produced increased and approximately 15% of the broilers produced in Denmark in 2018 were exported for slaughter. The production of turkeys has fluctuated considerably over the past decade. Since 2006, more than 99% of the turkeys produced have been exported for slaughter, thus the majority of turkey meat available for sale in Denmark is listed as imported.

3.2.2 Registered antimicrobial agents

Table 3.3 shows the antimicrobial agents registered to treat bacterial infections in humans and animals respectively. Some of these are listed on the highest priority list of critically important antimicrobial agents for the treatment of bacterial in-

fections in humans, according to definitions made by a working group under the World Health Organization [AGISAR, 6.revision, WHO 2019]. In order to be considered critically important, an antimicrobial must be the only- or one of a limited number of compounds available to treat serious human disease. Critically important antimicrobial agents are also used to treat diseases in food animals and pets, so the reservoir of resistance-potential bacteria is not restricted to humans only. Since bacteria may be transmitted from animals to humans, and bacteria that cause human disease are capable of acquiring resistance genes from bacteria of animal origin, resistance against the critically important antimicrobials can be spread widely.

In the newest revision from 2019 five drug classes were considered to be critically important:and of highest priority: fluoroquinolones, 3rd, 4th and 5th generation cephalosporins, macrolides, glycopeptides and polymyxins. In Denmark, in food animals the use of these drug classes has in general been low or been reduced through either voluntary or legislative restrictions, apart from macrolides, see chapter 4 for more information. For trends and traditions in the antimicrobial treatment of humans and information on the national action plan from 2017 see chapter 5.

Growth promoters are no longer used for animals in Denmark and are shown in parentheses in Table 3.3. Most of these influenced Gram-positive bacteria. Since 1995, the indicator enterococci from animals and meat have been used as a measure of resistance towards growth promoters.

Table 3.1 Production (1000' heads) of food animals and mink, Denmark DANMAP 2018

Year	Pigs		Cattle		Poultry		Fur animals - mink	
	Total	Exported[a]	Slaughter cattle	Dairy cows	Broilers	Turkeys	Females	Kits
2009	27603	6642	507	569	108851	1175	2675	14768
2010	28505	7074	519	574	117653	1184	2657	14638
2011	29399	7632	551	575	115454	960	2776	15325
2012	29047	8794	539	580	111080	1103	2936	16147
2013	28996	9318	551	574	117315	692	3143	17634
2014	29926	10517	556	563	115497	595	3296	17963
2015	30874	11563	513	561	114238	598	3387	18798
2016	31660	12771	540	571	120685	834	3161	17260
2017	31662	13679	509	570	117602	601	3410	18378
2018	32558	14028	533	575	122268	642	3385	17634

Source: Statistics Denmark (www.dst.dk) and Kopenhagen Fur. Export data for 15-50 kg live pigs from the Danish Agriculture and Food Council
a) Export of 15-50 kg live pigs. These are included in total number of heads

Table 3.2 Production (mill kg) of meat, milk and fish, Denmark DANMAP 2018

Year	Pork	Beef	Broiler meat[a]	Turkey meat	Milk	Farmed fish[b]	
						Fresh water	Marine
2009	1898	137	165	11	4734	29	11
2010	1974	142	178	14	4830	28	10
2011	2008	145	175	9	4801	28	11
2012	1902	138	168	12	4928	28	13
2013	1896	140	177	8	5025	28	12
2014	1924	143	174	9	5113	30	11
2015	1954	135	172	9	5278	32	12
2016	1943	142	182	10	5376	33	12
2017	1896	135	178	7	5478	33	14
2018	1966	141	185	10	5615	33	14

Source: Statistics Denmark (www.dst.dk) and The Danish AgriFish Agency.Export data for poultry from Statistics Denmark (personal communication)
a) Export data for poultry from Statistics Denmark (personal communication). Assumes a final slaughtered weight of 1.51 kg per broiler produced (Danish Agriculture and Food, 2013)
b) The numbers for 2018 are not final. The production of farmed fish includes fish transferred from one production facility to another

Table 3.3 Antimicrobial agents registered for systemic and veterinary intramammary therapeutic use in animals and humans, Denmark

DANMAP 2018

ATC / ATCvet codes [a]	Therapeutic group	Antimicrobial agents within the therapeutic groups	
		Animals	Humans
J01AA / QJ01AA, QJ51AA	Tetracyclines	Chlortetracycline, doxycycline, oxytetracycline	Doxycycline, lymecycline, tetracycline, tigecycline
QJ01BA	Amphenicols	Florfenicol	
J01CA / QJ01CA	Penicillins with extended spectrum	Ampicillin, amoxicillin	Ampicillin, pivampicillin, amoxicillin, pivmecillinam, mecillinam
J01CE / QJ01CE	Beta-lactamase sensitive penicillins	Benzylpenicillin, phenoxymethylpenicillin, procaine penicillin, penethamate hydroiodide	Benzylpenicillin, phenoxymethylpenicillin
J01CF / QJ51CF	Beta-lactamase resistant penicillins	Cloxacillin, nafcillin	Dicloxacillin, flucloxacillin
J01CR / QJ01CR	Comb. of penicillins and beta-lactamase inhibitors	Amoxicillin/clavulanate	Amoxicillin/clavulanic acid, piperacillin/tazobactam
J01DB / QJ01DB, QJ51DB	First-generation cephalosporins	Cefalexin, cefadroxil, cefapirin	Cefalexin, cefazolin
J01DC	Second-generation cephalosporins		Cefuroxime
J01DD / QJ01DD, QJ51DD	Third-generation cephalosporins incl. comb. with beta-lactamase inhibitors	Cefoperazone, ceftiofur, cefovecin	Cefotaxime, ceftazidime, ceftriaxone, ceftazidime/avibactam
J01DE / QJ51DE	Fourth-generation cephalosporins	Cefquinome	Cefepime
J01DF	Monobactams		Aztreonam
J01DH	Carbapenems		Meropenem, ertapenem
J01DI	Fifth-generation cephalosporins incl. comb. with beta-lactamase inhibitors		Ceftaroline fasamil, ceftolozan/tazobactam, ceftobiprol
J01EA	Trimethoprim and derivatives		Trimethoprim
J01EB / QJ01EQ	Short-acting sulfonamides	Sulfadimidine	Sulfamethizole
J01EE / QJ01EW	Comb.of sulfonamides and trimethoprim, incl. derivatives	Sulfadiazine/trimethoprim, sulfadoxine/trimethoprim, sulfamethoxasol/trimethoprim	Sulfamethoxazole/trimethoprim
J01FA / QJ01FA	Macrolides	Spiramycin, tylosin, tilmicosin, tylvalosintartrat, tulathromycin, gamithromycin, tildiprocin	Erythromycine, roxithromycine, clarithromycine, azithromycine, telithromycine
J01FF / QJ01FF	Lincosamides	Clindamycin, lincomycin	Clindamycin
QJ01XX [b]	Streptogramins	(Virginiamycin)	
J01GB / QJ01RA, QA07AA	Aminoglycosides	Streptomycin, dihydrostreptomycin, gentamicin, neomycin, apramycin	Tobramycin, gentamicin
J01MA / QJ01MA	Fluoroquinolones	Enrofloxacin, marbofloxacin, difloxacin, ibafloxacin, pradofloxacin	Ciprofloxacin, levofloxacin, moxifloxacin
QJ01MB	Other quinolones	Oxolinic acid	
QJ01MQ [b]	Quinoxalines	(Carbadox, olaquindox)	
J01XA, A07AA / Not in ATCvet [b,c]	Glycopeptides	(Avoparcin)	Vancomycin, teicoplanin, dalbavancin, oritavancin
J01XB / QA07AA [b]	Polypeptides (incl. polymyxins)	Colistin, bacitracin	Colistin
J01XC	Steroid antibacterials		Fusidic acid
J01XD,P01AB [c]	Imidazole derivatives		Metronidazole
J01XE	Nitrofurane derivatives		Nitrofurantoin
J01XX / QJ01FF	Other antibacterials	Spectinomycin	Methenamine, linezolid, daptomycin, tedizolide, fosfomycin
QJ01XQ	Pleuromutilins	Tiamulin, valnemulin	
QP51AG04	Antiprotozoals, sulfonamides	Sulfaclozine	
Not in ATCvet [b]	Oligosaccharides	(Avilamycin)	
Not in ATCvet [b]	Flavofosfolipols	(Flavomycin)	

a) ATCvet codes start with a Q
b) Animal growth promoters used before 1999 are listed in parentheses
c) Intestinal antiinfectives (A07AA) and imidazole derivatives for protozoal diseases (P01AB) were, for the first time, included in DANMAP 2014, since their widespread use in the treatment of *Clostridium difficile* infections makes them belong to the most used antibiotics in human infections in Denmark