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SUMMARY



2. Summary

The Danish integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) was founded in 1995, providing a unique one-health surveillance system for the continuous surveillance and research of antimicrobial consumption and resistance. A key objective of the DANMAP programme is to provide an evidence base for decision-making and to further understand the associations between antimicrobial usage (AMU) and the occurrence of antimicrobial resistance (AMR) across populations.

In Denmark, antibiotics for humans and animals are available by prescription only, and all prescriptions are recorded by the Register of Medicinal Statistics. The data are available for surveillance, control programmes and research through national databases called Medstat and Vetstat. The registration covers the whole nation and dates back to the mid-90s (Medstat) and 2000 (VetStat), respectively.

DANMAP 2019 analyses all records of the types and amounts of antimicrobials prescribed for animal and human treatment in Denmark during 2019 and compares it with historic data. It also analyses susceptibility testing data of isolates obtained from hospitals, general practice, veterinary practice, food-industry laboratories and the Danish Veterinary and Food Administration.

Human isolates cover bacteraemias, urinary tract infections and gastroenteritis caused by the most important pathogenic bacteria. Isolates from animals are collected in accordance with the EU harmonised monitoring of antimicrobial resistance in zoonotic and commensal bacteria [Decision 2013/652/EU].

Statens Serum Institut (SSI) collates and interprets data from the human sectors and the Technical University of Denmark (DTU) collates and interprets data from the food and animals sectors. In the chapter of zoonoses, the data is integrated and interpreted together.

Antimicrobial consumption in animals

Annual consumption of antimicrobials in animals is based on the amount of veterinary prescription medicine registered by pharmacies, private companies, veterinarians and feed mills. In DANMAP, the antimicrobial use in animals is estimated first as kg active compound and further as the number of standardised maintenance doses per day (DADDs). Trends in antimicrobial usage in pigs, cattle, and fur animals are presented in DAPD, which is the “proportion of population in treatment per day” estimated as number of DADD per 1,000 animals per day.

The total use of antimicrobials in animals amounted to approximately 97 tonnes of active ingredients in 2019, 3% less than in 2018. This is the lowest amount since 2002. A consistently

decreasing trend has been observed since 2013. In 2019, 30 tonnes less was used than in 2010 (-24%).

The pig sector used approximately 75% of all veterinary-prescribed antimicrobials, equal to 72.6 tonnes active compound. Adjusting for changes in production and export of pigs in 2019, an estimated 2.3% of all pigs received antimicrobial treatment per day (23 DAPD), similar to the level in 2018. In weaner pigs, the annual use in 2019 compared to 2018 was reduced from 91 to 89 DAPD. However, in finishers it increased from 17 to 18 DAPD, while it remained similar to 2018 levels for sows and piglets (19 DAPD).

The use of medical zinc decreased by 7%, from 509 to 475 tonnes from 2018 to 2019, and the industry is still preparing for the EU withdrawal in June 2022.

The types of antimicrobials used in pigs changed notably. The use of tetracycline in pigs has decreased significantly since 2009, mainly from 2016 to 2019 as a response to the differentiated Yellow Card initiative. Similarly, colistin use was phased out by 2017. During the same period, discernible, but smaller, increases in the use of macrolides and aminoglycosides occurred, especially in weaners.

The overall use of antimicrobials in cattle has fluctuated between 12 and 13 tonnes over the past five years. In 2019, more than two thirds of the amount was used to treat older cattle (>1 year) and 4% of this amount was for intramammary treatment. The antimicrobial use for older cattle has decreased from 3.9 to 3.2 DAPD (-18%) over the past decade, while the use for younger cattle (<1 year) has increased from 5.2 to 7.3 DAPD (+39%).

Antimicrobial use in poultry was relatively low. Since 2015, the antimicrobial use in poultry decreased every year, however, in 2019 the use increased from 1,326 kg to 1,612 kg. The use of antimicrobials in the aquaculture industry decreased from 3,557 kg in 2018 to 2,522 kg in 2019, which probably reflects the relatively cold summer in 2019. Increased focus on prudent use combined with low occurrence of disease resulted in an observed 40% reduction in antimicrobial use for fur animals in 2018. In 2019, the use was 3,955 kg, which is 36% lower than in 2017, and is equivalent to a treatment proportion in the mink population of approximately 3% (32 DAPD).

Since 2011, there has been an overall decreasing trend in the use of antimicrobials in dogs and cats, with a marked reduction in the use of cephalosporins. However, critically important antimicrobials are still used in companion animals, and all fluoroquinolones and more than half of the cephalosporins used in animals are prescribed for dogs and cats.

Antimicrobial consumption in humans

Information on consumption in humans is based on total sales from primary pharmacies and hospital pharmacies, reported in volume per package size and transformed into defined daily doses (DDD), the assumed average maintenance dosage per antimicrobial drug as defined by the WHO ATC Center. Data has been reported from primary health care since 1994 and from hospital care since 1997. As per first of January 2019, the WHO ATC Center changed DDD values for several antibiotics, based on recommendations and results from an expert working group. From DANMAP 2018, the new DDD values were applied and all tables and figures were updated ten years back.

For comparison with actual treatment dosages used in Denmark, the DANMAP 2019 also presents consumption in Danish adjusted daily doses (DaDDD) for the primary sector and the hospital sector, respectively. When applying DaDDD, the share of each antibiotic class changed notably and was more correctly resembled in the total, overall showing a smaller use than with the standard DDD. However, to enable comparison with other countries standard DDDs as defined by the WHO were primarily used in the report.

In 2019, **total consumption** of antimicrobials in humans (primary sector and hospital sector combined) was 15.76 DDD per 1000 inhabitants per day (DID), lower than the consumption in 2018 (15.97 DID) and lower than a decade ago in 2010 (18.31 DID). The highest consumption ever reported in Denmark was in 2011 (18.95 DID). In 2010, the consumption of antimicrobial agents in **primary sector** was 16.56 DID, which since decreased to 13.76 DID in 2019 (-17%). The **hospital sector** simultaneously saw an increase from 1.65 DID in 2010 to 1.93 DID in 2019 (17%). When applied and corrected for hospital activity, total antimicrobial consumption at hospitals was 107 DDD per 100 bed-days (DBD) and 306 DDD per 100 admissions (DAD), a rise from 100 DBD and 296 DAD the previous year. From 2010 to 2019, the total consumption at hospitals increased by 49% and 21%, when measured in DBD and DAD, respectively. The proportion of antimicrobial agents prescribed by hospital doctors and redeemed at primary pharmacies increased from constituting 13.1% of the consumption in primary health care in 2015 to constitute 16.7% in 2019 (measured in DID).

Decreases in the past ten years described for the primary sector were observed for all age groups (but less pronounced for the eldest >80 years) and for both genders, regardless of the indicators used. However, the consumption in the 15-19 year olds increased by 3.5% since 2018, primarily driven by an increase in the consumption of tetracyclines. The biggest decrease in consumption the last decade was observed in the youngest (0 to 4 year olds), where the number of treated patients per 1000 inhabitants decreased by 41%. In 2019, there were 262 treated patients per 1000 0-4 year olds corresponding to 435 prescriptions redeemed per 1000 inhabitants.

Comparison of consumption by gender showed that in females, the number of treated patients per 1000 inhabitants decreased by 25% and in males by 28% the last decade. In 2019, the average number of treated patients (regardless of age) was 277 females per 1000 inhabitants and 191 males per 1000 inhabitants. This corresponds to 541 redeemed prescriptions per 1000 inhabitants for females and 347 redeemed prescriptions per 1000 inhabitants for males.

Penicillins remained the most frequently used antimicrobial agents in both primary health care (65%) and hospital care (55%), but the changes in consumption observed within this drug group in the last decade continued. Thus in 2010, beta-lactamase sensitive penicillins constituted 53% of all penicillins consumed in primary health care (5.26 DID of 9.91 DID), while in 2019 this had decreased to 38% (3.44 DID of 8.98 DID). Simultaneously, consumption of combination penicillins increased markedly in both sectors. In 2019, combination penicillins constituted 4.6% of the antimicrobial consumption in primary health care and 16% of the consumption in hospital care. From 2018 to 2019, decreased consumption in primary health care and increased consumption in hospital care were observed for most penicillins.

In Denmark, fluoroquinolones, cephalosporins and carbapenems are defined as **antimicrobials of critical interest** (cephalosporins and carbapenems are only used at hospitals). In 2019, the consumption of the three drug classes constituted altogether 18% of the total consumption at hospitals, a decrease from 20% observed the year before, and a decrease from 31% in 2010. Carbapenems increased from 2.83 DBD in 2018 to 2.99 DBD in 2019 (5.9%) whereas cephalosporins decreased from 10.24 DBD in 2018 to 9.29 DBD in 2019 (-9.2%). Fluoroquinolones continued the decreasing trend observed since 2015. In 2019, fluoroquinolones accounted for a consumption of 6.95 DBD, corresponding to 6.5% of the total consumption at hospitals (7.18 DBD and 7.1% in 2018). In primary care, fluoroquinolones accounted for 0.37 DID equivalent to 2.7% of the total consumption in 2019.

Resistance in zoonotic- and indicator bacteria

Isolates from animals and meat for susceptibility testing are mainly collected by repeated representative, national surveys conducted at Danish slaughterhouses and at retail. Isolates from humans are from clinical investigations, submitted to Statens Serum Institut for further typing.

In Denmark, antimicrobials are generally not recommended for treatment of self-limiting diarrhoea in humans including salmonellosis and campylobacteriosis. In prolonged or severe cases, treatment may be required and in these cases macrolides (azithromycin) and in hospital settings, ciprofloxacin are recommended. Macrolides are used to treat infections in animals in Denmark, whereas fluoroquinolones and cephalosporins are not used in food-producing animals.

Erythromycin (macrolide) resistance was present in 4% of *Cam-pylobacter jejuni* isolates from humans with a known travel history. Erythromycin resistance was not observed in human isolates from domestic infections, Danish broiler meat, broilers and cattle. Resistance to quinolones remained common in *C. je-juni* isolates from humans, broiler meat, broilers and cattle. The levels of ciprofloxacin resistance was 70% in human isolates and 45% and 65% in broilers and meat hereof, respectively. Resistance towards ciprofloxacin were often accompanied by tetracycline resistance and 51% of the human isolates, and 39% and 30% of the broiler and broiler meat isolates, respectively, were tetracycline resistant.

Salmonella isolates from pigs and Danish pork were included in DANMAP 2019, and *S. Derby* and *S. Typhimurium* remained the most prevalent serotypes. The level of azithromycin resistance in *Salmonella Typhimurium* isolates was 1% in human isolates and 3% in isolates from Danish pork. Among human cases, resistance to fluoroquinolones was observed in 14% of *S. Typhimurium* isolates from travel-related cases and in 5% of the isolates from domestically acquired cases. Fluoroquinolone resistance has not been recorded in *S. Typhimurium* from Danish pigs and pork since 2010 and 2007, respectively. Resistance to 3rd generation cephalosporins and carbapenems was not observed in *S. Typhimurium* isolates from animals, food and domestically acquired human cases. Two percent of *S. Typhimurium* from travel-associated cases were resistant to 3rd generation cephalosporins. Carbapenem resistance was not observed.

Surveillance of resistance in animal pathogens was expanded to include pathogens from small animals and mastitis pathogens in addition to the usual porcine pathogens. Within all populations and pathogens, resistance levels remained fairly stable during the years of analysis.

In 2019, trends and levels of antimicrobial resistance in **indicator *E. coli*** from poultry, pigs and cattle were overall very similar to previous years.

The relative distribution of fully sensitive indicator *E. coli* from broilers (64%) and cattle (87%) was comparable to 2018, whereas a decrease from 53% to 42% was observed in fully sensitive isolates from pigs. Compared to 2018, a statistically significant increase (from 30% to 44%) in sulfonamide resistance and a moderate increase (from 23% to 32%) in occurrence of multidrug-resistance was observed in pig isolates. Among broiler and cattle isolates, the occurrence of multidrug-resistance was comparable to 2018 and only minor fluctuations (1%-2%) in resistance were observed between the years in cattle isolates. However, over the last 5-year period, the occurrence of multidrug-resistant *E. coli* isolates from broilers has decreased significantly (from 23% to 11%).

From broilers, one isolate (<1%) resistant to cefotaxime and ceftazidime was detected by the non-selective method. More

phenotypic resistant isolates were detected by the more sensitive selective isolation methods in samples from pigs and cattle, indicating that resistance was present in a small proportion of commensal *E. coli* in pigs and cattle as well. Furthermore, no colistin, meropenem and tigecycline resistance was detected. The slow but steady increase in resistance to ciprofloxacin/nalidixic acid in *E. coli* from broilers, observed over the last ten years, continued.

In 2019, selective isolation methods showed that occurrence of **ESBL/AmpC-producing *E. coli*** in animals and meat aligned with trends observed from 2015-2018: lower occurrence in cattle compared to pigs (8% vs. 27%), lower levels in domestically produced broiler meat and pork than in imported (5% and 3% vs. 34% and 42%, respectively), and a continued decreasing occurrence in Danish broiler meat. ESBL transferring enzymes often associated with human infections, such as CTX-M-1, CTX-M-14 and/or CTX-M-15 were detected in low or very low numbers in all sources, and chromosomal AmpC mutations in isolates from pigs and cattle were still dominant.

Importantly, again all samples examined for carbapenemase-producing *E. coli* (including OXA-48) were found negative.

In 2019, **enterococci** from pigs showed no resistance to vancomycin, linezolid, teicoplanin or tigecycline. The *E. faecalis* isolates were resistant to tetracycline (91%), erythromycin (63%) and chloramphenicol (33%), and compared to 2017 increases in tetracycline (13%) chloramphenicol (9%) and erythromycin (8%) resistance were observed. Resistance levels in *E. faecium* were comparable to the latest observations from 2010-2012 and the most commonly observed resistance was to tetracycline (54%), erythromycin (20%) and ampicillin (12%).

Currently, the zoonotic risk linked to transfer of resistance to critically important antimicrobials from animals to humans appears to be very limited in Denmark.

Resistance in human clinical bacteria

The national surveillance of resistance in human clinical bacteria are from two sources. Firstly, data from routine diagnostics performed at the 10 departments of clinical microbiology (DCMs) in Denmark extracted from the Danish Microbiology Database (MiBa). Secondly, isolates submitted to the reference laboratories at SSI due to voluntary extended surveillance of specific species and/or types or as mandatory surveillance of notifiable diseases under the Danish Health Authority.

Surveillance based on MiBa data

Since the beginning of DANMAP and particularly during the past decade the number of human invasive infections under surveillance has increased remarkably with 46% (8,021 cases in 2010 to 11,712 cases in 2019). The number of blood cultures taken as registered in MiBa increased equivalently with 113,986 unique patients' blood cultured in 2010 compared to 169,231 patients in 2019 an 48% increase.

For *Escherichia coli*, the number of invasive cases increased from approximately 61.8 cases per 100,000 inhabitants in 2010 to 96.7 cases in 2019. A slow but steady increase in resistance to cephalosporins (cefuroxime and/or 3rd generation cephalosporins) was observed for both invasive cases and urinary cases through the decade. Increased resistance to piperacillin-tazobactam was observed from 2018 (3.8% in invasive cases) to 2019 (5.5% in invasive cases). No increases in the numbers of carbapenem resistant clinical *E. coli* cases were observed in 2019.

For *Klebsiella pneumoniae*, the number of invasive cases increased from approximately 14.4 cases per 100,000 inhabitants in 2010 to 23.4 cases in 2019. The general trends for both invasive and urinary cases were declines in resistance rates to important antimicrobials as cephalosporins, gentamicin and ciprofloxacin through the beginning of the decade, slowing down or stagnating during the past five years. An increase in resistance to piperacillin-tazobactam was observed with 8.7% resistance reported in invasive cases in 2019 compared to 6.1% in 2018.

Regarding invasive *Pseudomonas aeruginosa* the situation in Denmark is quite stable both in the number of cases and resistance profiles, with relatively low overall prevalence of resistance. The highest level of resistance was reported for ciprofloxacin with 5.5%. Meropenem resistance was reported in 3.1% of the cases, and in only 1.7% of the cases, resistance to three or more of the five antimicrobials under surveillance were reported. None of the invasive *P. aeruginosa* isolates were registered as colistin resistant.

Approximately one invasive case of *Acinetobacter species* per 100,000 inhabitants was observed in 2019 corresponding to a low number of 72 invasive cases in total. Of these, five isolates were resistant to ciprofloxacin, two were resistant to gentamicin and none was resistant to meropenem or had combined resistance to ciprofloxacin and gentamicin.

The number of invasive cases of *Enterococcus faecium* increased from 9.4 cases per 100,000 inhabitants in 2010 to 13.6 cases in 2018 followed by a small decrease to 12.7 cases in 2019. For invasive *Enterococcus faecalis*, the number remained stable with 10.7 cases per 100,000 inhabitants in 2010 and 10.9 cases in 2019. Over the decade, there has been an alarming increase in invasive cases of vancomycin-resistant and -variable *E. faecium*. While 0.5% of invasive *E. faecium* were reported vancomycin resistant in 2008, this rate increased to 12% in 2018, but with a small decrease to 11% in 2019.

Surveillance based on data from the reference laboratories

Since 2014, the DCMs have voluntarily submitted 3rd generation cephalosporin resistant *E. coli* isolates from bloodstream infections to SSI for characterisation. In 2019, a total of 375

E. coli isolates from bloodstream infections were identified with phenotypic test as **ESBL, AmpC or carbapenemase-producing** isolates. As in previous years, CTX-M-15 was the most prevalent resistance-transferring enzyme, although a decrease in prevalence was observed compared to 2018, while the prevalence of CTX-M-14 and CTX-M-55 increased. In 2019, a new *E. coli* ST23 CTX-M-14 -producing clone was reported by seven of the ten DCMs, primarily from emergency departments.

In recent years, the DCMs have voluntarily submitted carbapenem-resistant isolates (both clinical and screening) for verification and genotyping at the National Reference Laboratory for Antimicrobial Resistance at SSI. As of 5 September 2018, the Danish Health Authority made **carbapenemase-producing organisms (CPO)** notifiable. During 2019, 221 CPOs were detected from 187 patients compared with 177 CPOs from 160 patients in 2018, equivalent to a 25% overall increase of submitted CPO isolates compared to 2018. More than one isolate from the same patient were included in DANMAP, if the isolates belonged to different bacterial species and/or if the isolates harboured different carbapenemases. The 221 CPOs consisted of 194 CPEs, 20 *Acinetobacter* spp. and seven *Pseudomonas* spp. New patients were registered in 16 ongoing CPE outbreaks in 2019.

In recent years, *E. faecium* isolates harbouring the *vanA* gene complex, but phenotypically vancomycin susceptible, have been reported from different countries. These enterococci are referred to as **vancomycin-variable enterococci (VVE)**. In 2017, VVE isolates were included in the voluntary **vancomycin-resistant Enterococcus (VRE)** surveillance. However, VVE diagnostics differ substantially between the different regions and an underestimation of the prevalence could exist. Furthermore, not all VRE/VVE isolates are received at SSI, and for the 2016 to 2019 reports, the number of submitted isolates was supplemented with the number of VRE/VVE registered in MiBa. This resulted in a total of 660 VRE/VVE isolates from 660 patients in 2019 compared to 603 VRE isolates from 599 patients in 2018. Since 2013, a steep increase in clinical VRE isolates has been observed. Until 2018 the increase has mostly been seen for *vanA E. faecium*, but during 2019, an increase was also detected for *vanB E. faecium*.

Streptococcus pneumoniae from invasive pneumococcal disease (IPD) and resistance towards penicillin and erythromycin have been included in DANMAP since the beginning. Of the 600-800 cases annually, bacteraemia is most common and meningitis only counts for 40-60 of the cases. Antimicrobial susceptibility in *S. pneumoniae* is closely related to serotypes. The distribution of IPD-associated serotypes are again influenced by the PCV vaccines, introduced in the childhood immunisation programme in Denmark in 2007 and enforced in 2010. Some serotypes also have natural cycles over the years. In 2019, 623 cases of IPD from blood or spinal fluid were registered and isolates were received from 606 of the cases. The dominant serotype was serotype 8 (26.7%) and they were

all found susceptible to both penicillin and erythromycin. In total, susceptibility to penicillin was 95.1% susceptible, 4.2% susceptible increased exposure and 0.7% resistant. For erythromycin, 96.6% were susceptible and 3.4% were resistant.

The surveillance of invasive infections caused by **beta-haemolytic streptococci (BHS)** in Denmark is based on voluntary submission of invasive isolates from the DCMs. During the last five years, the number of received isolates of BHS from unique cases of infection has increased from 556 in 2014 to 873 in 2018, followed by a minor decrease to 838 in 2019. The corresponding changes for individual serogroups were: group A, -18%; group B, -2%; group C, +5% and group G, +0.3%. All isolates were susceptible to penicillin. The erythromycin resistance rate as well as the clindamycin resistance rate remained unchanged compared to 2018 for all four serogroups.

Surveillance of invasive ***Haemophilus influenzae*** is mandatory for type b, but isolates of all types are voluntarily submitted to the reference laboratory at SSI. In 2019, 114 cases of invasive *H. influenzae* were identified. This is at the same level as previous years, which ranged from 106 to 128 cases in the period from 2014 to 2018. Of the 114 cases, isolates from 100 cases were received for serotyping and antimicrobial susceptibility testing at SSI and data were supplemented with registered cases in MiBa. The majority of cases were non-capsular (78%), and six isolates were of type b. Resistance to penicillin was observed in 29% of the cases and 24% were resistant to ampicillin, 14% to cefuroxime and 11% to amoxicillin-clavulanic acid, which is similar to data from 2018. Whole-genome sequencing data was available from 93 isolates, and nineteen of these possessed the TEM-1 gene for beta-lactamase. None had the ROB-1 gene.

The number of bloodstream infections with ***Staphylococcus aureus*** was 2,233 cases in 2019 compared to 2,276 cases in 2018; 2.1% of cases were methicillin-resistant (MRSA). Resistance to other antimicrobials remained at the same level as in previous years. The number of new **methicillin-resistant *Staphylococcus aureus* (MRSA)** cases (colonisation or infection) was 3,657 in 2019, close to the number in 2018 (3,669). The number of cases acquired in hospitals (HA-MRSA) remained at a low level (75 cases in 2019); whereas community acquired (CA-) MRSA continued to increase (1,536 in 2019). The number of livestock-associated (LA-) MRSA CC398 decreased to 1,122 cases from 1,215 in 2018 and most of these were found in patients with contact to livestock production (89%). The number of LA-MRSA infected persons without livestock contact was 86 in 2019 and has been stable in recent years, indicating low secondary transmission.

The national surveillance of antimicrobial resistance in ***Neisseria gonorrhoeae*** in Denmark is based on the voluntary submission of gonococcal isolates from the DCMs. From 2011 to 2016, the annual number of received isolates increased, followed by a decrease in 2017 and 2018, and a slight increase in 2019. Concomitantly with these changes, the rate of ciprofloxacin resistance decreased to 18% in 2016 and increased to 41% in 2019 (40% in 2018). Ceftriaxone resistance has not been observed in Denmark, apart from one case in 2017 with a marginally increased MIC (0.25 mg/L).

Future improvements and developments

DANMAP demonstrates that a well-established integrated surveillance programme is important to understand the development of AMR and to point out where prudent use of antimicrobials is necessary.

Antimicrobial use in humans and food animals is relatively low and well regulated in Denmark compared to many other countries in the EU and the rest of the world. This contributes to fairly stable resistance patterns in production animals and in Danish meat compared to the big reductions observed when growth promoters were banned in the 90s.

Over the last decade, we have observed increasing numbers of multi-resistant bacteria in humans and introduction of new critical resistance types such as different ESBLs in food animals and Danish meat. International travel and trade plays an important part in introducing new bacteria and resistance in the Danish populations, where they may propagate and spread. Monitoring critically resistant bacteria such as MRSA, ESBL, CPE and VRE in all relevant reservoirs provides essential information on when and where control measures are needed.

This DANMAP report provides a robust overview of the status on antimicrobial use and antimicrobial resistance in Denmark in 2019 from a One Health perspective. The long history of the report adds certainty to its conclusions, whilst the DANMAP programme continues to evolve and develop as new opportunities and challenges appear.



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INTRODUCTION TO DANMAP