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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 platform 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).

In Denmark, antibiotic treatment - of both humans and animals - is available by prescription only, and all prescriptions are recorded by the Register of Medicinal Statistics and available through national databases (MEDSTAT and VetStat). The registration is very detailed, covers the whole nation and dates back to the mid-90s (Medstat) and 2000 (VetStat), respectively.

The report DANMAP 2018 summarises the results of susceptibility testing of isolates obtained from hospitals, general practice, veterinary practice, food-industry laboratories and the Danish Veterinary and Food Administration; as well as records of the types and amounts of antimicrobials prescribed for animal and human treatment in Denmark during 2018. Human isolates cover all bacteraemias caused by the most important pathogenic bacteria, based on all available microbiological data on the first isolate per species per patient per year, representing complete data from all of Denmark. Also included, are microbiological data on *Escherichia coli* and *Klebsiella pneumoniae* isolates from urinary tract infections from hospitals and from general practitioners. In addition, the report includes results from typing and characterisation based on whole genome sequencing of isolates from reportable diseases or isolates carrying specific resistance mechanisms that were received at the reference laboratories. Since 2014, *Campylobacter*, *Salmonella* and indicator and ESBL/AmpC-producing *E. coli* from production animals and meat are collected in accordance with the EU harmonised monitoring of antimicrobial resistance in zoonotic and commensal bacteria [Decision 2013/652/EU]. Furthermore, isolates collected from additional surveys and isolates from *Salmonella* control programmes are also included

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.

Antimicrobial consumption in animals

Information on consumption in animals is based on total amount of veterinary prescription medicine as registered by pharmacies, private companies, veterinarians and feed mills. Detailed data for each prescription item are sent to the VetStat database, and the antimicrobial use in animals is estimated

first as kg active compound and further transformed into defined animal daily doses (DADD), a national veterinary equivalent to the international defined daily doses (DDD) system applied in the human field.

Since 2013, there has been an overall decreasing trend in the use of antimicrobials in animals and in 2018 the use had been reduced by 14%, a reduction of almost 17 tonnes, compared with the antimicrobial use in 2013. The total use of veterinary prescribed antimicrobials amounted to just around 100 tonnes in 2018.

Patterns in antimicrobial use in animals are driven by the pig sector, because 75% of all antimicrobials used in animals are used for pigs, equivalent to 74.7 tonnes in 2018. Measured in DADD per 1000 animals per day (DAPD), the antimicrobial use in weaner pigs was reduced from 97 to 91 DAPD, meaning that on a given day in 2018, on average, approximately 9% of weaner pigs received antimicrobial treatment. In finishers, the use was reduced from 18 to 17 DAPD, while it remained at roughly the same level in sows and piglets, around 19 DAPD. The overall use for pigs, measured in DAPD and adjusted for changes in exports was reduced by approximately 4% from 24 to 23 DAPD in 2018, and has decreased by 32% since 2009.

The types of antimicrobials used in pigs also shifted notably. Since 2009, the use of tetracyclines in pigs reduced significantly and especially from 2016 to 2018, due to the implementation of the differentiated "Yellow card".

The differentiated "Yellow Card" initiative has also resulted in a close to zero use of colistin, since the first quarter of 2017. However, in weaners the decrease in the use of tetracyclines and colistin was somewhat mirrored by increases in the use of macrolides, pleuromutilines and aminoglycosides.

The overall use for cattle has fluctuated between 12 and 13 tonnes over the past five years. In 2018, more than two thirds were used to treat older cattle (>1 year) and approximately 500 kg were used as intramammary treatment. Measured in DAPD, the antimicrobial use for older cattle (>1 year) has decreased from 4 to 3 DAPD (-13%) over the past decade, while the use for younger cattle (<1 year) has increased from around 5 to 7 DAPD (+43%).

Antimicrobial use in poultry is relatively low (1,326 kg). Notable fluctuations may occur as a result of disease outbreaks in a few large flocks, which was the case in 2014 and 2015. However, since 2015, the use has been reduced each year and was 16% lower than in 2015. In contrast, the use of antimicrobials in the aquaculture industry more than doubled (1,860 kg more) in 2018 due to the very warm summer in 2018.

From 2014 to 2017, the use of antimicrobials in fur animals (mink) increased. However, in 2018 the industry increased focus on prudent use and developed an action plan to reduce the use within the production. The increased focus combined with low occurrence of disease in 2018 resulted in a 40% reduction in antimicrobial use for fur animals (2,467 kg less) compared with 2017.

Companion animals still use more critically important antimicrobials compared to other species. Almost all fluoroquinolones and more than half of the cephalosporins used in animals are used in dogs and cats. Despite a small increase in use from 2015 to 2016, there has been an overall decreasing trend in the use of antimicrobials in dogs and cats since 2011. In addition, the antimicrobial use in pets appears to have shifted away from the use of cephalosporins towards the broad spectrum penicillins.

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 given antimicrobial class as defined by the WHO ATC Center. Data from primary health care has been reported since 1994 and from hospitals 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. In DANMAP 2018, the new DDD values were applied and all tables and figures updated ten years back.

In 2018, consumption of antimicrobials in humans in total, primary sector and hospital sector combined, was 15.95 DDD per 1000 inhabitants per day (DID), lower than the consumption in 2017 (16.67 DID) and lower than a decade ago in 2009 (17.47 DID). The highest consumption ever reported in Denmark was in 2011 (18.91 DID).

In 2009, the consumption of antimicrobial agents in the primary sector was 15.69 DID, which since decreased to 13.98 DID in 2018 (-11%). The hospital sector simultaneously saw an increase from 1.67 DID in 2009 to 1.92 DID in 2018 (15%).

For comparison with actual treatment dosages used in Denmark, the report also includes two figures presenting consumption in Danish adjusted daily dosage (DaDDD) for the primary sector and the hospital sector, respectively. When applying DaDDD, figures changed notably and the share of each antibiotic class was more correctly resembled in the total, overall showing a smaller use than with the standard DDD. For most figures in the report the standard DDD as defined by the WHO were used for comparison with other countries.

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. The biggest decrease was observed in the youngest (0 to 4 year olds), where the number of treated patients per 1000 inhabitants of the same age group decreased with 41%. In 2018, there were 272 per 1000 treated 0 to 4 year olds corresponding to 406 prescriptions redeemed per 1000 inhabitants.

In women, the number of treated patients per 1000 inhabitants decreased with 16% and in men with 20%. In 2018, the average number of patients treated (regardless of age and gender) was 243 per 1000 inhabitants corresponding to 459 prescriptions redeemed per 1000 inhabitants. When the number of prescriptions issued through hospital doctors is subtracted from the total number, the average number of treated patients (all age groups and genders) was 236 per 1000 inhabitants corresponding to 396 prescriptions redeemed per 1000 inhabitants.

The total antimicrobial **consumption at hospitals** was measured at 99 DBD and 292 defined daily doses per 100 admissions (DAD), respectively, a rise from 96 DBD and 282 DAD the previous year. From 2009 to 2018, the total consumption at hospitals increased with 41% and 10%, when measured in DBD and DAD, respectively.

Penicillins remained the most frequently used antimicrobial agents in both primary health care (66%) and in hospital care (54%), but the changes in consumption observed within this drug group in the last decade continued. Thus in 2009, beta-lactamase sensitive penicillins constituted 54% of all penicillins consumed in primary health care (5.31 DID of 9.45 DID), while in 2018 this had decreased to 39% (3.61 DID of 9.22 DID). Simultaneously, consumption of combination penicillins increased markedly in both sectors for that decade. Thus in 2018, combination penicillins constituted 4.7% of the antimicrobial consumption in primary health care and 16% of the consumption in hospital care. From 2017 to 2018, decreases in the consumption of most penicillins were observed.

Together with the penicillins with extended spectrum, combination penicillins were in 2018 the largest antimicrobial drug group consumed at hospitals.

In Denmark, **fluoroquinolones, cephalosporins and carbapenems** are defined as antimicrobials of critical interest and cephalosporins and carbapenems are only used at hospitals. In 2018, the consumption of the three drug classes constituted altogether 20% of the consumption at hospitals, a decrease from 23% observed the year before, and a larger decrease from 32% in 2009. Carbapenems decreased from 2.83 DBD in 2017 to 2.77 DBD in 2018, a decrease of 2.3 %. Cephalosporins decreased from 2.83 DBD in 2017 to 2.77 DBD in 2018, a decrease of 16%. This decrease was expected since the consumption increased during 2017 due to a shortage of piperacillin with tazobactam.

Fluoroquinolones continued the decreasing trend observed since 2013, but with more pronounced reductions for the last three years. In 2017, fluoroquinolones accounted for a consumption of 6.98 DBD, corresponding to 7.9% of the total consumption at hospital. In 2018, this had decreased to 6.81 DBD, corresponding to 7.2% of the consumption at hospitals. In primary care, fluoroquinolones accounted for 0.41 DID equivalent to 3.0% of the total consumption in 2018.

Resistance in zoonotic- and indicator bacteria

In Denmark, antimicrobials are generally not recommended for treatment of diarrhoea including salmonellosis and campylobacteriosis, due to the self-limiting nature of the diseases. If needed, it is recommended that patients are treated with macrolides (azithromycin and erythromycin).

Isolates from animals and meat for susceptibility testing are mainly collected by repeated, representative, national surveys conducted at Danish slaughter houses.

Resistance to quinolones remained the most common resistance type found in *Campylobacter jejuni* from all populations: broilers, cattle and humans. Around one third of all isolates of animal origin and domestically acquired human cases were resistant to ciprofloxacin, whereas 83% of the travel associated human isolates were ciprofloxacin resistant. The majority of ciprofloxacin resistant isolates from poultry and humans were also resistant to tetracycline and over the last ten years resistance to both tetracycline and ciprofloxacin increased in broilers. No erythromycin resistance was found in *C. jejuni* isolates from animals or human patients in 2018.

Salmonella isolates from pigs and Danish pork were included in DANMAP 2018, and *S. Derby* and *S. Typhimurium* remained the most prevalent serotypes. The resistance profiles were dominated by a large proportion of monophasic *S. Typhimurium* isolates, exhibiting resistance to tetracycline, ampicillin and sulfonamides. The trend in resistance to these three antimicrobials has been increasing steadily with approximately 30% increase since 2009. Resistance to ciprofloxacin and 3rd generation cephalosporins was present in low levels in human isolates and not found in pigs or Danish pork. In 2018, the level of azithromycin resistance in *S. Typhimurium* isolates from humans was less than 1%, and only 5% in Danish pork.

In 2018, the most prominent changes in resistance in indicator *Escherichia coli* from food-producing animals were a reduced occurrence of multidrug-resistance in isolates from broilers and pigs and an increase in fully susceptible isolates from pigs compared to previous years. Resistance patterns and levels in indicator *E. coli* from poultry, pigs and cattle were overall similar to previous years. No resistance to cefotaxime and ceftazidime was detected when using the non-selective isolation method and no resistance to colistin, meropenem and tigecycline was found.

Imported chicken meat was more likely to contain **ESBL/AmpC-producing *E. coli*** than Danish meat and broilers. The levels were comparable to those of 2016. The most common ESBL/AmpC enzymes identified across the broiler sources were again the AmpC enzyme, CMY-2 and the ESBL enzyme, CTX-M-1. As previously, all samples examined for carbapenemase-producing *E. coli* (including OXA-48) were found negative.

Resistance in human clinical bacteria

The national surveillance of resistance in human clinical bacteria, is based on either data from routine diagnostics performed at the 10 departments of clinical microbiology (DCMs) in Denmark, or on resistance and typing results from isolates received at the reference laboratories at SSI for further characterisation. Isolates are received either based on a mutual agreement on voluntary submission of specific species and/or types of resistances or as part of a mandatory surveillance program of diseases made notifiable by the Danish Health Authority. In DANMAP 2018, data from the 10 DCMs were extracted directly from the Danish Microbiology Database (MiBa).

Resistance in human clinical bacteria -surveillance based on MiBa data

Since the beginning of DANMAP and particularly during the past decade the number of human invasive infections has increased remarkably. The number of blood cultures taken as registered in the Danish Microbiology Database increased equivalently.

For *Escherichia coli*, the number of invasive cases increased from approximately 61.8 cases per 100,000 inhabitants in 2010 to 93.4 cases in 2018. Until 2017, the resistance trends were rather stable despite the increasing number of invasive cases. However, the resistance trends for cephalosporins in invasive *E. coli* reversed in 2017 and continued these slight increases also in 2018. In addition, an increasing trend in cephalosporin resistance was observed for urinary cases coinciding with an increasing total number of urinary cases from primary Health, from approximately 30,000 cases in 2010 to 80,000 cases in 2018. As for blood cultures taken, the increase in the number of positive urine samples equalled an increase in the total number of urine samples from primary health care submitted for culturing at the DCMs.

For *Klebsiella pneumoniae*, the number of invasive cases increased from approximately 14.4 cases per 100,000 inhabitants in 2010 to 22.1 cases in 2018. Figures and time trend analyses revealed that resistance rates have decreased markedly over the past 10 years for gentamicin, ciprofloxacin, cefuroxime and 3rd generation cephalosporins, but with lesser or insignificant decreases for the past five years. For urinary cases, the notable increase in resistance rates for mecillinam and sulfonamide observed in 2017 was repeated in 2018 with approximately the same resistance rates (16-17% for mecillinam and 22-25% for sulfonamide) as in 2017. In 2018, rather

steep increases in resistance to piperacillin/tazobactam and ciprofloxacin were observed in urinary cases as well.

Regarding resistance in invasive *Pseudomonas aeruginosa*, the situation in Denmark remained stable with resistance rates below 5% to ciprofloxacin, gentamicin, ceftazidime, meropenem and piperacillin/tazobactam. The number of invasive cases has also remained relatively stable but with a small increase during the last four years from approximately seven cases per 100,000 inhabitants in 2014 to 8.5 cases in 2018.

For *Acinetobacter species* the total number was approximately one invasive case per 100,000 inhabitants in 2018 corresponding to a low total number of 55 invasive cases. Of these, two cases had combined resistance to ciprofloxacin, gentamicin and meropenem and further two cases were resistant to ciprofloxacin only and one case to gentamicin only.

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. For invasive *Enterococcus faecalis* the number has remained stable with 10.7 cases per 100,000 inhabitants in 2010 compared with 10.5 cases in 2018. An alarming increase in invasive cases of vancomycin-resistant and -variable *E. faecium* was observed. While 0.5% of invasive *E. faecium* were reported vancomycin resistant in 2008, this rate had increased to 12% in 2018. Part of the increase was due to the detection and spread of vancomycin-variable *E. faecium* since 2017.

Resistance in human clinical bacteria -surveillance based on data from the reference laboratories

Since 2014, the Danish departments of clinical microbiology have voluntarily submitted 3rd generation cephalosporin resistant *E. coli* isolates from bloodstream infections, for characterisation to SSI. In 2018, 24 different ESBL-, pAmpC- and carbapenemase-enzymes were detected among the 352 **ESBL- and pAmpC-producing *E. coli* from bloodstream infections**. As in previous years, CTX-M-15 was the most prevalent enzyme, with a significant increase from 164 cases in 2017 to 200 cases in 2018 ($p = 0.032$), whereas the presence of CTX-M-14 and CTX-M-55 decreased significantly from 48 and 13 cases in 2017 to 31 and 4 cases in 2018, respectively. In five cases, a carbapenemase-enzyme was detected along with an ESBL-enzyme. The most common sequence type (ST) was ST131 (54%), followed by ST69 (8%) and ST38 (6%).

In recent years, Danish departments of clinical microbiology have voluntarily submitted carbapenem resistant isolates (both clinical and screening) for verification and genotyping at the National Reference Laboratory for Antimicrobial Resistance at SSI. The Danish Health Authority made **carbapenemase-producing organisms (CPO)** notifiable as of September 5th 2018. During 2018, 177 CPOs were detected from 160 patients compared with 123 CPOs from 115 patients in 2017, equivalent to a 44% overall increase of submitted CPO isolates

compared to 2017. More than one isolate from the same patient were included, if the isolates belonged to different bacterial species and/or if the isolates harboured different carbapenemases. The 177 CPOs consisted of 153 CPEs (mainly *E. coli*, *K. pneumoniae* and *Citrobacter freundii*), 18 *Acinetobacter* spp. and three *Pseudomonas* spp. Several outbreaks with CPE were seen during 2018.

In recent years, *E. faecium* harbouring the *vanA* gene complex, but phenotypically vancomycin susceptible, has been described in different countries. These enterococci are referred to as **vancomycin-variable enterococci (VVE)**. In 2017, VVE isolates were included in the **vancomycin-resistant enterococcus (VRE)** surveillance. However, VVE diagnostics differ substantially in the different regions. For the 2017 and 2018 reports, the number of submitted isolates was supplemented with the number of VRE/VVE registered in the Danish Microbiological Database (MiBa), which resulted in a total of 600 VRE/VVE isolates from 599 patients in 2018 compared to 510 VRE isolates from 508 patients in 2017. From 2013, a steep increase in clinical VRE isolates has been observed. The increase has mostly been seen for *vanA E. faecium*. In 2017, the VVE clone ST1421-CT1134 *vanA E. faecium* accounted for 3% of the *E. faecium* isolates. In 2018, 34% ($n = 173$) of the *vanA E. faecium* isolates belonged to ST1421-CT1134.

During 2015-2018, eight **linezolid resistant *E. faecium* (LRE)** isolates and eight **linezolid resistant *E. faecalis* (LRE)** isolates were sent to SSI (only one isolate per patient were included). No **linezolid-vancomycin resistant *E. faecalis* (LVRE)** were detected, whereas, six linezolid-vancomycin resistant *E. faecium* (LVRE) were detected. The findings of LRE and LVRE are of concern. Linezolid is used for treatment of VRE. Only a limited number of antimicrobial agents are available for treatment of infections with LVRE.

Streptococcus pneumoniae causes close to eight hundred cases of invasive pneumococcal disease (IPD) annually in Denmark, of which bacteraemia are the most frequent and meningitis counts for 50-60 of the cases. DANMAP has included data on susceptibility for IPD on penicillin and erythromycin from 1990 and onwards. Non-susceptibility to both penicillin and erythromycin increased gradually from less than 1% in the early nineties to 5-6% in recent years. Non-susceptibility to penicillin has varied without a clear pattern throughout the past six years and was 3.8% in 2018. Only one isolate (0.1%) was resistant to penicillin in 2018. The level of erythromycin non-susceptibility has decreased steadily since 2014 and reached 2.5% in 2018. Antimicrobial susceptibility in *S. pneumoniae* is closely related to serotypes. The prevalence of IPD-associated serotypes are also influenced by the PCV vaccines, which were introduced in the childhood immunization programme in Denmark in 2007. The large variation in antimicrobial susceptibility in IPDs seen in recent years is most likely driven by changes in serotype prevalence due to the effect of vaccines and by the natural cycles of different serotypes.

The surveillance of invasive infections caused by **beta-haemolytic streptococci (BHS)** in Denmark is based on voluntary submission of invasive isolates from the departments of clinical microbiology. During the last five years, the number of isolates of BHS has increased from 556 in 2014 to 873 in 2018. The corresponding increases for individual serogroups were: group A; 36%, group B; 32%, group C; 51%, and group G; 30%. The erythromycin resistance rate showed a small increase from 2014 to 2018 for groups A and G, while a small decrease was observed for groups B and C. The clindamycin resistance rate increased for groups A and G but was unchanged for groups B and C. All BHS isolates, irrespective of serogroup, were fully susceptible to penicillin.

Surveillance of invasive ***Haemophilus influenzae*** is mandatory for type b, but the majority of isolates of all types are voluntarily submitted to the reference laboratory at SSI. Serotyping is performed at SSI while the data for antimicrobial susceptibility is collected through MiBa. 121 cases were identified in 2018 of which 17% were type b and the majority (73%) were non-capsular. Susceptibility data are described in this report for the five most frequently tested antimicrobials. Of the isolates with available data for susceptibility in MiBa, 26% were registered as resistant to penicillin, 1% to ciprofloxacin, 20% to ampicillin, 16% to cefuroxime and 10% to amoxicillin/clavulanic acid. One hundred isolates were received at SSI, and 17 of these possessed the TEM-1 gene for beta-lactamase.

The number of bloodstream infections with ***Staphylococcus aureus*** increased from 2,104 cases in 2017 to 2,276 cases in 2018, of which 1.6% were methicillin-resistant (MRSA). Resistance to penicillin has decreased slowly during the last decade and was 72% in 2018.

The number of new **methicillin-resistant *Staphylococcus aureus* (MRSA)** cases was 3,669 in 2018, a small increase from 2017 (3,579 new cases). The number of livestock-associated MRSA CC398 was 1,215 (1,212 in 2017) and most of them were found in patients with contact to livestock production.

The national surveillance of antimicrobial resistance in ***Neisseria gonorrhoeae*** in Denmark is based on the voluntary submission of gonococcal isolates from the departments of clinical microbiology. From 2011 to 2016 the annual number of received isolates increased followed by a decrease in 2017 and 2018. Concomitantly with these changes, the rate of ciprofloxacin resistance decreased to 18% in 2016 and increased to 40% in 2018. Ceftriaxone resistance has never been diagnosed in Denmark, except from one case in 2017 with a marginally increased MIC (0.25 mg/L).

Future improvements and developments

DANMAP demonstrates that a well-established 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 EU and the rest of the world. This contributes to relatively 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 such as ESBL 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 be maintained 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 2018. 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.