



DANMAP Seminar 2024

Danish Programme for surveillance of antimicrobial consumption and resistance in bacteria from food animals, food and humans



Dagens program

10.30-10.45 Velkomst v. Henrik Ullum, Direktør v. Statens Serum Institut

- 10.45-12.00 DANMAP highlights v. redaktørteamet
 - Majda Attauabi, Statens Serum Institut
 - Ute Wolff Sönksen, Statens Serum Institut
 - Vibe D Andersen, DTU Fødevareinstituttet
 - Ana Sofia Ribeiro Duarte, DTU Fødevareinstituttet
 - Joana Pessoa, DTU Fødevareinstituttet
 - Jesper Larsen, Statens Serum Institut

12.00-12.30 Frokost

- 12.30-13.30 Nuværende udfordringer i behandling af mennesker og dyr med antibiotika
 - John Haugegaard, Den Danske Dyrlægeforening
 - Thomas Loof Hedegård & Bjarne Mikladal Christensen, Amgros
- 13.30-14.45 Tema: Hvordan bruges DANMAP i virkelighedens verden Poll: Evaluering af anvendeligheden af DANMAP
- 14.45-15.00 Afslutning og tak for i dag v. Ute Wolff Sönksen og Ana Sofia Ribeiro Duarte

Seminaret faciliteres af Ute Wolff Sönksen, Fagchef for AMR overvågningen, Statens Serum Institut

DANMAP highlights

- Antimicrobial consumption in humans
- Resistance in human pathogens
- Antimicrobial consumption in animals
- Resistance in zoonotic bacteria
- Resistance in indicator bacteria
- Resistance in animal pathogens

IMAP





DANMAP Seminar 2024

Antibiotikaforbrug til mennesker



Majda Attauabi Cand.pharm

Ute Wolff Sönksen Chief Physician

Statens Serum Institut

Agenda

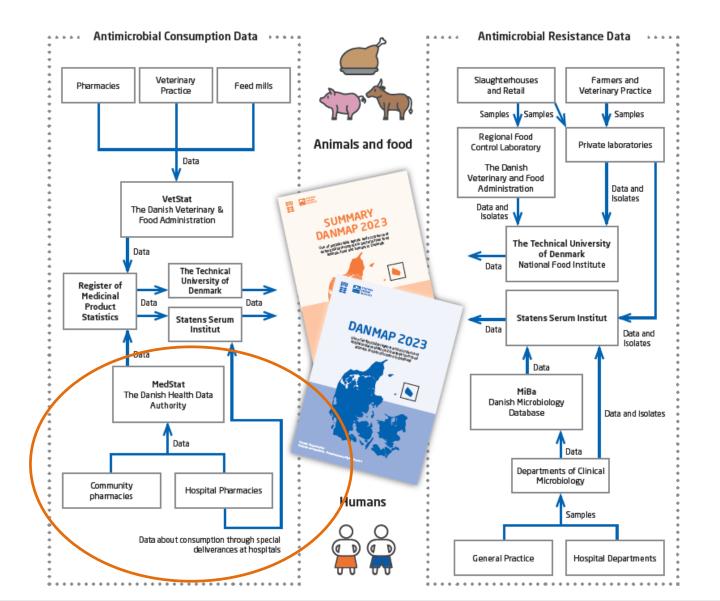


- Antimicrobials in Denmark
 - Characteristics
 - AWaRe classification
 - International comparison
- Antimicrobials in primary health care
 - Age groups
 - Indications
- Antimicrobials at hospitals
 - Trends over time
 - Shortages
- Topics in focus



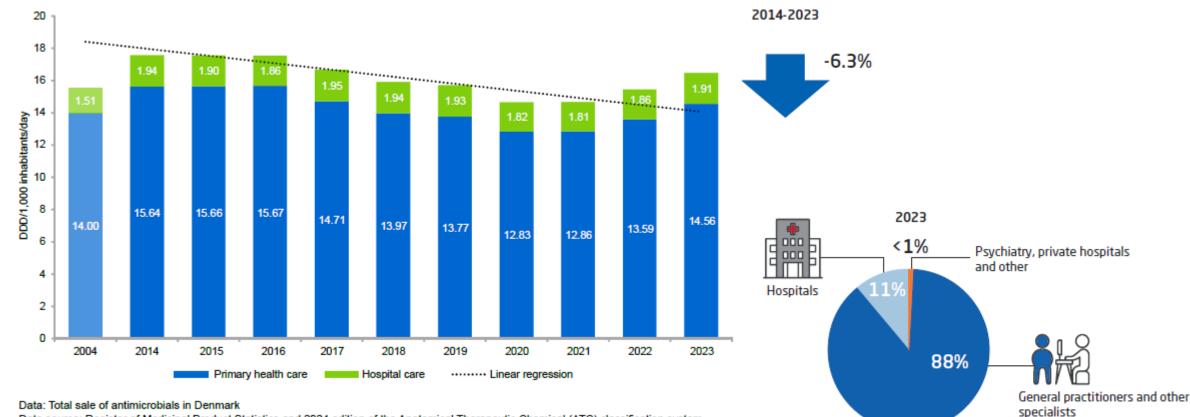


DANMAP data flow



Antibiotic consumption in Denmark

DANMAP 2023



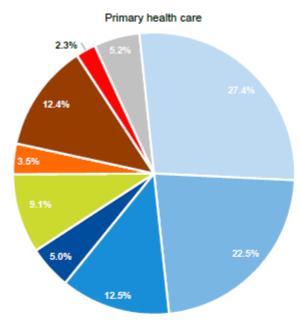
Data source: Register of Medicinal Product Statistics and 2024 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.1 Total consumption of systemic antimicrobial agents in humans, DDD per 1,000 inhabitants per day, Denmark, 2004 and

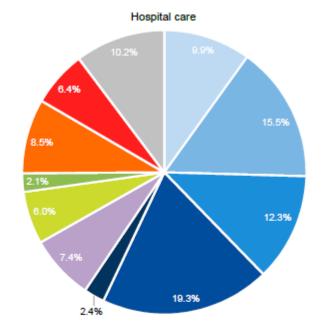
2014-2023

Consumption is characterised by a big share of penicilias

Figure 5.4 Percentage distribution of antimicrobial agents in primary health care and hospital care, DDD, Denmark, 2023 DANMAP 2023



- Beta-lactamase sensitive penicillins (J01CE)
- Penicillins with extended spectrum (J01CA)
- Beta-lactamase resistant penicillins (J01CF)
- Comb. of penicillins, incl. beta-lactamase inh. (J01CR)
- Carbapenems (J01DH)
- Cephalosporins (J01DB, DC, DD)



- Macrolides, lincosamides and streptogramins (J01F)
- Aminoglycosides (J01G)
- Sulfonamides and trimethoprim (J01E)
- Tetracyclines (J01AA)
- Fluoroquinolones (J01MA)
- Other antimicrobials (J01A, DF, X, P01AB)

Data: Registered sale of antimicrobials to individuals and antimicrobial consumption at somatic hospitals Data source: Register of Medicinal Product Statistics and 2024 edition of the Anatomical Therapeutic Chemical (ATC) classification system

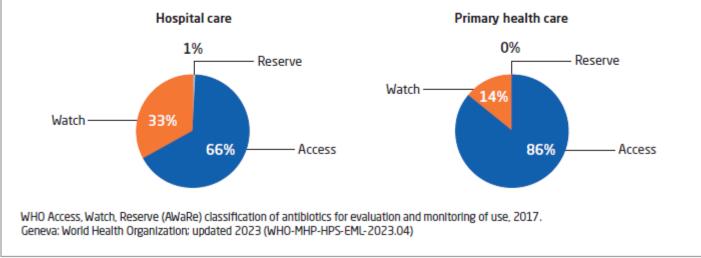


... and a big share of "Access" antibiotics

AWaRe classification of antimicrobials in Denmark, 2023

The World Health Organization (WHO) has developed the AWaRe classification system as a tool to assist antibiotic stewardship and to reduce antimicrobial resistance. Antibiotics are classified into three groups to emphasise the Importance of their appropriate use:

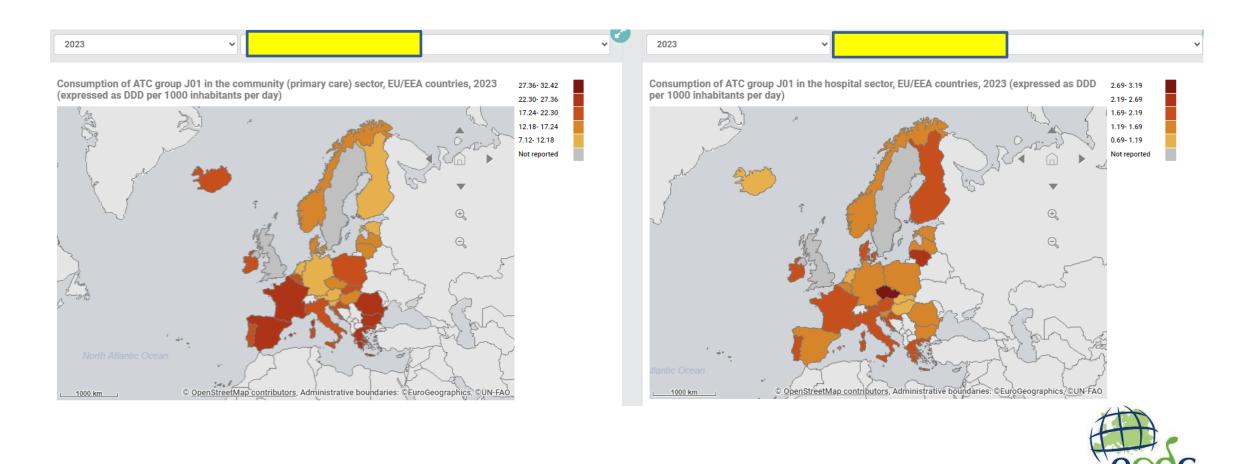
- Access: Antibiotics used to treat common susceptible pathogens with lower resistance potential than antibiotics in the other groups. 60% of total antimicrobial consumption should consist of Access agents.
- Watch: Antibiotics that have higher resistance potential, including most of the highest priority agents. These antibiotics should be prioritised as key targets of stewardship programs and monitoring.
- Reserve: Antibiotics reserved for treatment of confirmed or suspected infections due to multidrug resistant organisms. These antibiotics should be considered as "last resort" options.







Denmark compared to EU



Source: European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA (ESAC-Net) - Annual Epidemiological Report 2023. Stockholm: ECDC; 2024.

DISEASE PREVENTION



 Table 2. Total consumption (community and hospital sectors combined) of antibacterials for systemic use (ATC group J01), EU/EEA countries, 2019–2023 (expressed as DDD per 1 000 inhabitants per day)

Country	2019	2020	2021	2022	2023	Trend 2019—203	23	Change (%) 2019- 2023	Recommended reduction (%) 2019-2030	2023	Targe 2030
Austria	11.6	8.8	8.8	10.5	11.3			-3%	-3%	11.3	11.2
Belgium	21.4	16.7	17.4	20.5	20.6	\searrow		-3%	-18%	20.6	17.5
Bulgaria	20.7	22.7	24.4	25.7	26.3		Î	+27%	-18%	26.3	17.0
Croatia	18.8	15.7	18.2	20.2	21.2	\checkmark		+13%	-9%	21.2	17.1
Cyprus	30.1	28.9	25.0	33.5			N/A	N/A	-27%	N/A	22.0
Czechia	15.9	13.4	13.7	17.1	18.1	$\overline{}$		+7%	-9%	18.1	15.4
Denmark	15.3	14.3	14.4	15.2	16.2	\smile		+6%	-9%	16.2	13.9
Estonia	11.8	10.5	10.1	12.4	12.7	\smile		+8%	-3%	12.7	11.4
Finland	14.7	11.9	11.3	12.5	12.9	$\overline{}$		-12%	-9%	12.9	13.3
France	25.1	20.3	21.5	24.3	24.1	\searrow		-4%	-27%	24.1	18.3
Germany					13.3		N/A	N/A	-9%	13.3	11.5
Greece"	34.1	28.1	23.5	32.9	28.5		N/A	-16%	-27%	28.5	24.9
Hundary	14.4	11.2	11.9	14.4	14.2	$\overline{}$		-2%	-9%	14.2	13.1
Iceland	19.3	16.5	16.8	18.6	18.5	\sim		- 4%	N/A	18.5	N/A
Ireland	22.8	18.6	17.8	23.1	22.4	\sim		-2%	-27%	22.4	16.6
Italy	21.7	18.4	17.5	21.9	23.1	\checkmark		+6%	-18%	23.1	17.8
Latvia	13.9	11.9	11.6	14.9	14.9	\sim		+7%	-9%	14.9	12.6
Lithuania	16.3	14.2	14.1	18.5	18.7	\sim		+15%	-9%	18.7	14.6
Luxembourg*	21.1	16.1	15.9	19.1	20.2		N/A	-4%	-18%	20.2	17.3
Malta	20.7	16.6	15.8	24.0	22.9	\sim		+11%	-18%	22.9	17.0
Netherlands	9.5	8.5	8.3	9.1	9.6	\sim		+1%	-3%	9.6	9.2
Norway	14.9	13.9	14.0	15.3	15.5	\sim		+4%	N/A	15.5	N/A
Poland	23.6	18.5	20.2	23.6	23.2			-2%	-27%	23.2	17.3
Portugal	19.3	15.2	15.3	18.8	19.7	\sim		+2%	-9%	19.7	17.6
Romania	25.8	25.2	25.7	27.6	27.4	\sim		+6%	-27%	27.4	18.8
Slovakia	19.3	14.4	16.0	20.8	20.1	\sim		+4%	-9%	20.1	17.6
Slovenia	13.0	10.2	10.2	12.4	13.4	\sim		+3%	-9%	13.4	11.8
Spain	24.9	19.7	20.0	23.2	24.1	\sim		-3%	-27%	24.1	18.2
Sweden	11.8	10.3	10.1	11.2			N/A	N/A	-3%	N/A	11.4
EU/EEA**	19.8	16.4	16.4	19.3	19.9	\sim		+1%	N/A	19.9	N/A
EU***	19.9	16.4	16.4	19.4	20.0	\sim		+1%	-20%	20.0	15.9

Consumption of ATC group J01 in the community (prim (expressed as DDD per 1000 inhabitants per day)

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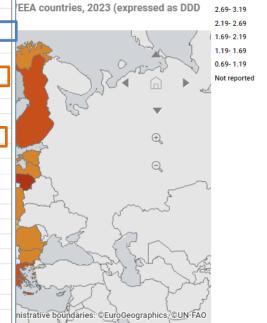
2023



Source: European Centre for Disease Progress towards EU target:

- Annual Epidemiological Report 202

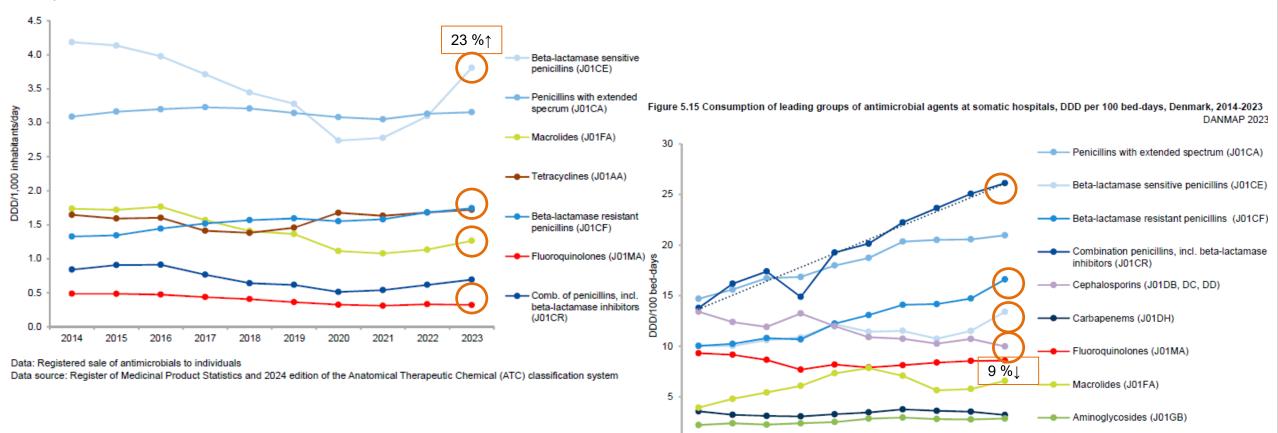
_	-		-								
			Incr	ease		Decr	ease				
2											
-	<u>≥</u> 20%	15% to <20%	10% to <15%	5% to <10%	1% to <5%	-1% to <-5%	-5% to <-10%	-10% to <-15%	-15% to <-20%	Target reached	
	* As per t approach				n on step	ping up l	EU action	s to com	bat antim	icrobial resistance in a One Health	





Consumption trends for antimicrobials groups

Figure 5.8 Consumption of leading antimicrobial groups for systemic use in primary health care, DDD per 1,000 inhabitants per day, Denmark, 2014-2023 DANMAP 2023



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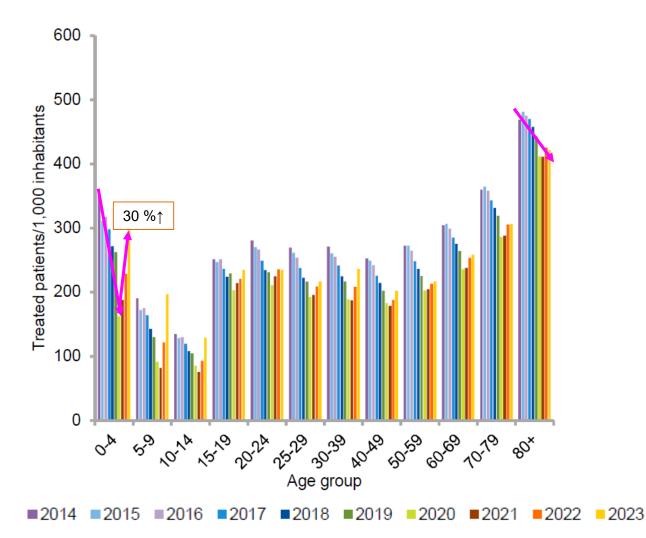
Data source: Register of Medicinal Product Statistics, 2024 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register

^{20&}lt;sup>14</sup> 20¹⁵ 20¹⁵ 20¹⁴ 20¹⁵ 20¹⁶ 20¹⁵ 20¹⁵ 20¹⁵ 2

Data: Antimicrobial consumption at somatic hospitals



Who is treated most frequently?



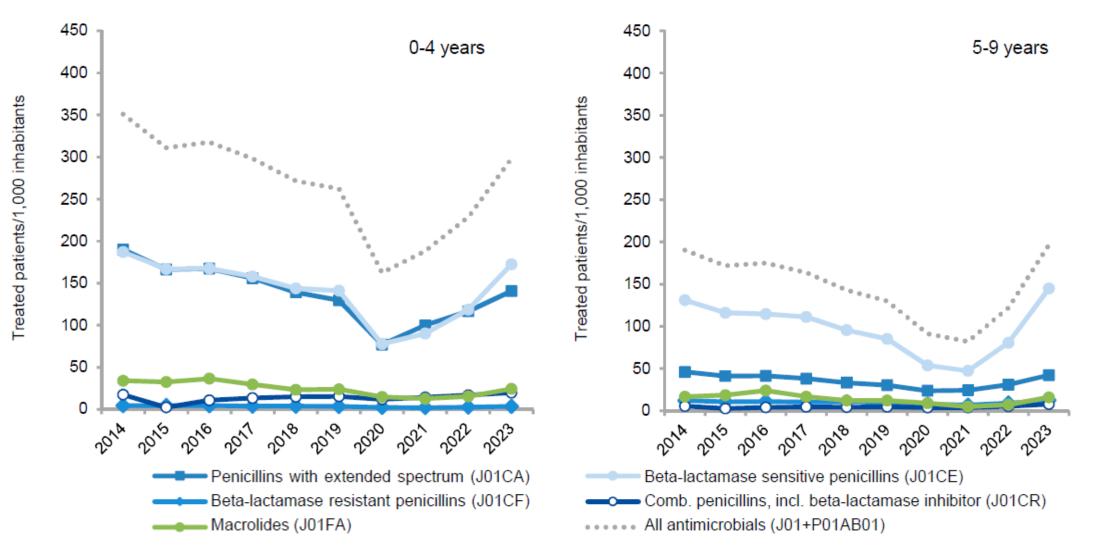


Data: Registered sale of antimicrobials to individuals

Data source: Register of Medicinal Product Statistics, 2024 edition of the Anatomical Therapeutic Chemical (ATC) classification system and Statistics Denmark

Antimicrobials for children

Figure 5.10 Consumption of main antimicrobial agents by age group, treated patients/1,000 inhabitants, Denmark, 2014-2023 DANMAP 2023

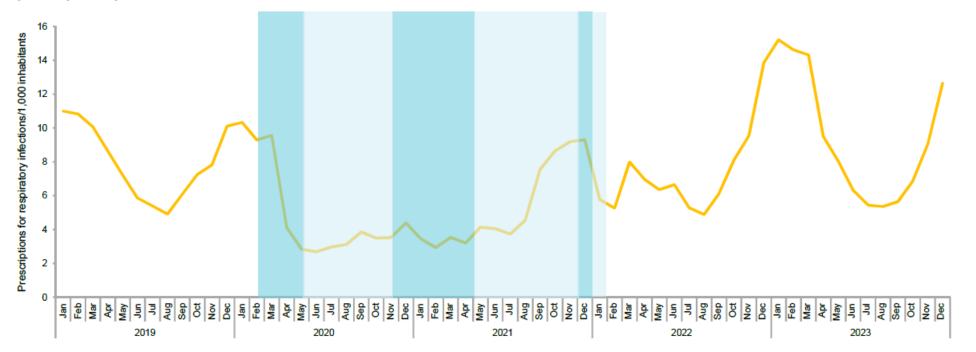






Antimicrobials for respiratory infections

Figure 5.12 Monthly antimicrobial prescriptions indicated for treatment of respiratory tract infections in primary health care, prescriptions per 1,000 inhabitants, Denmark, 2019-2023 DANMAP 2023



COVID-19 restrictions in place

Fewer restrictions in place

Data: Registered sale of antimicrobials to individuals

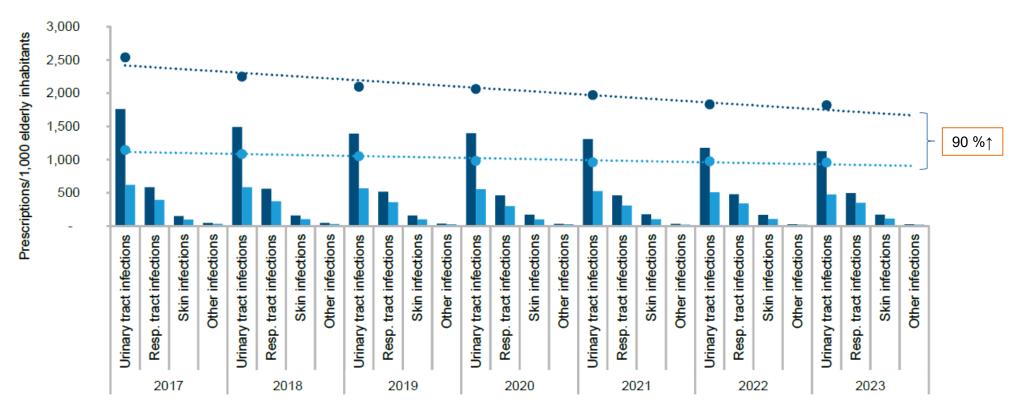
Data source: Register of Medicinal Product Statistics and 2024 edition of the Anatomical Therapeutic Chemical (ATC) classification system





Antimicrobials for elderly inhabitants

Figure 5.13 Consumption of antimicrobials (J01 and P01AB01) in primary health care for elderly inhabitants living in long term care facilities and for elderly inhabitants living in their own homes, Denmark, 2017-2023 DANMAP 2023



Elderly inhabitants living in long term care facilities

Elderly inhabitants living in their own homes

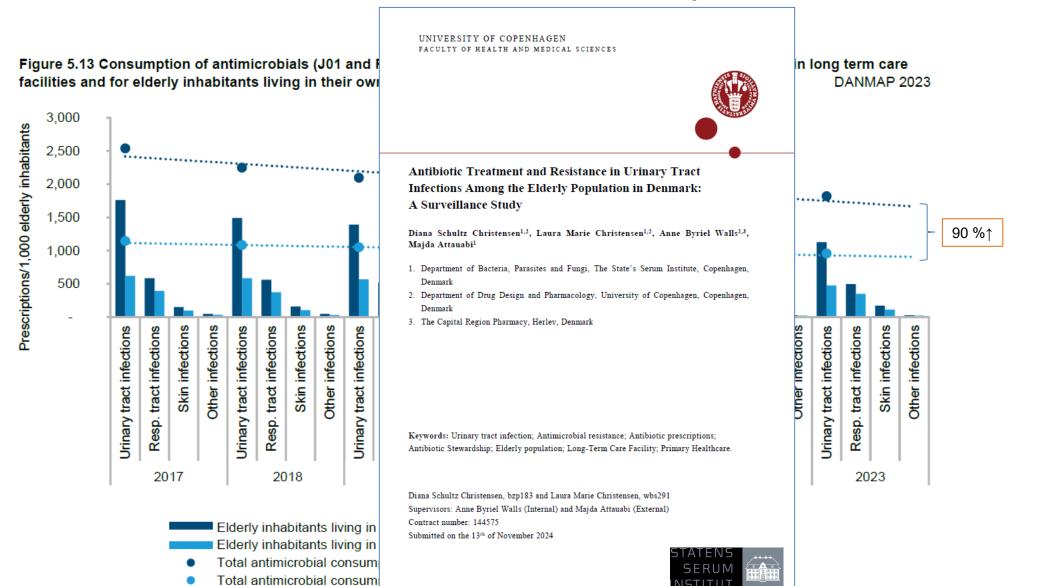
Total antimicrobial consumption for elderly inhabitants living in long term car

Total antimicrobial consumption for elderly inhabitants living in their own hor NST





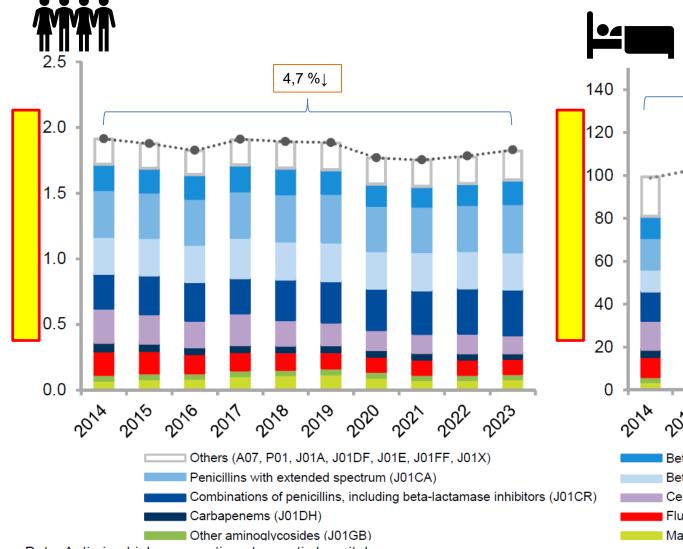
Antimicrobials for elderly inhabitants

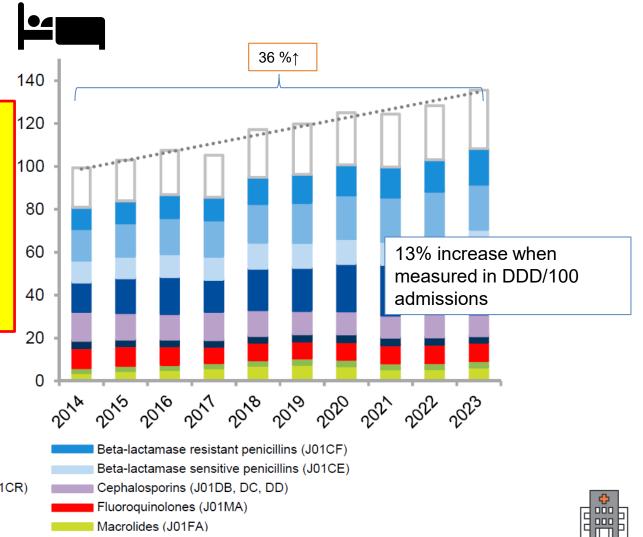






Antimicrobials at hospitals

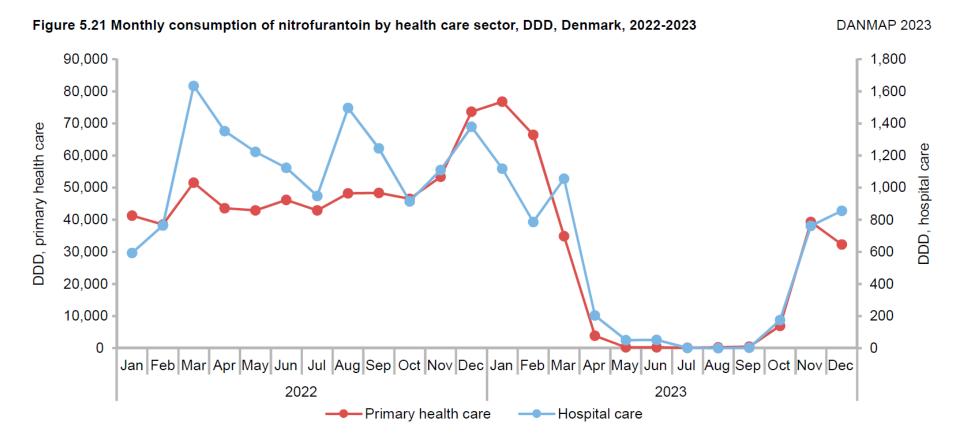




Data: Antimicrobial consumption at somatic hospitals

Data source: Register of Medicinal Product Statistics, 2024 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register

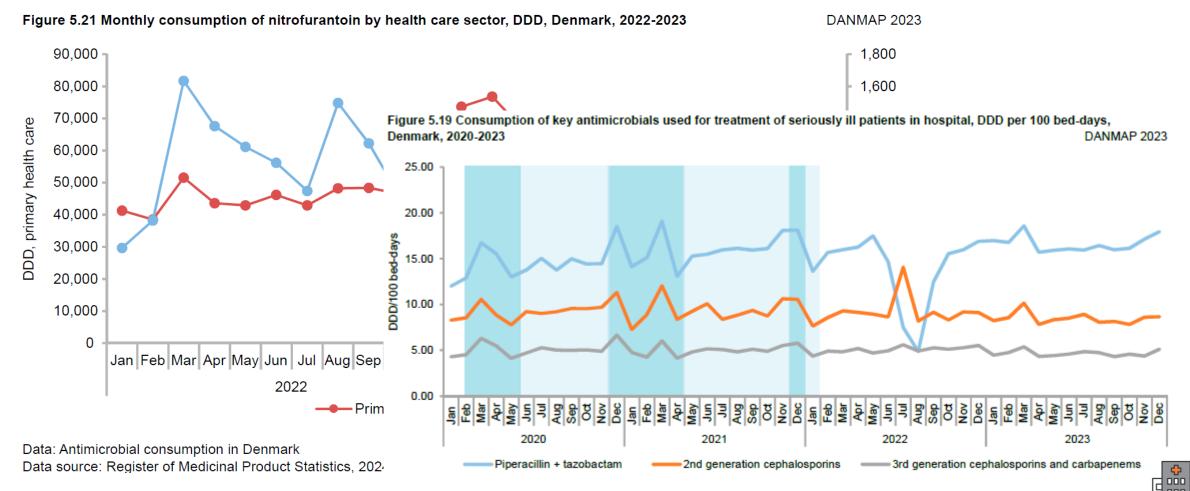
Shortages challenge supply of antimicrobials



Data: Antimicrobial consumption in Denmark Data source: Register of Medicinal Product Statistics, 2024 edition of the Anatomical Therapeutic Chemical (ATC) classification system



Shortages challenge supply of antimicrobials



Data: Antimicrobial consumption at somatic hospitals

Data source: Register of Medicinal Product Statistics, 2024 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register



Shortages challenge supply of antimicrobials

					Ye	ear				
Antimicrobial	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
J01MA12 Levofloxacin	4,470	7,240	8,080	8,180	6,710	7,360	20,370	44,200	41,530	45,360
J01XE01 Nitrofurantoin									(7,950
J01EE01 Sulfamethoxazol and trimethoprim	6,820	6,590	6,704	8,188	7,596	7,136	3,094	8,585	2,610	3,760
J01CE02 Phenoxymethylpenicillin				5,085	417			5,183		2,792
J01GB01 Tobramycin						6,895	6,840	4,790	3,850	2,620
J01CF05 Flucloxacillin	2,690	2,313	2,275	2,200	1,783	1,790	1,665	1,873	2,540	2,233
J01CR02 Amoxicillin and beta-lactamase inhibitor	721	10,743	3,276	2,579	3,882	4,348	4,277	3,934	4,177	1,726
J01MA02 Ciprofloxacin	710	1,155	1,195	690	766	726	1,028	908	935	890
J01CR05 Piperacillin og beta-lactamaseinhibitor			(16,465	4,457			(63,808)
J01CE08 Benzathine benzylpenicillin	316	562	372	1,514	618	538	748	544	524	652

Data: Consumption of antimicrobials on special delivery Data source: Danish Hospital Pharmacies



Topics in focus

Textbox 5.1		Textbox 5.3					
International approach to	o imț	Infection Prevention and Control and prevention of Antimicrobial					
What makes a market vulnerable? Which factors need repeated shortages and length of shortages are not ne		Resistance goes hand in hand					
elevated risk of withdrawal ¹ . The deregistration will be mentioned here, but it's a multifactual		In Denmark there are numerous activities concerning infection prevention and control (IPC) and antimicrobial resistance (AMR) - both on the national and on the international level.					
Textbox 5.2		Across Europe as well as globally it is increasingly stressed that controlling AMR in human health must be based on aligning ef-					
HALT 4 - An audit on ir	Textb	ox 5.4	titut si.dk				
among residents in Da	Cons	sumption of antimicrobials in the Faroe Islands					
HALT 4 (<u>https://hygiejne.ssi.dk/overvaagr</u> Facilities 4) is a European project manage	Backgr	ound oe Islands (FI) consist of 18 islands inhabited by approximately 54,000 inhabitants, approximately 22,000 of whom					
In 2023, the National Center for Infection	live in t	ne capital Tórshavn. Sjúkrahúsverkid consists of the main hospital (Landssjúkrahúsid, LS, with 130 beds), located in					
	iorshav	n, and two smaller hospitals in ^K Elsebeth Tvenstrup Jensen, Ann Winther Jensen, Anne Kjerulf, Lena Lambaa, and Marianna Konoy For further information: Elsebeth Tvenstrup Jensen, etj@ssi.dk and Anne Kjerulf, alf@ssi.dk					

In conclusion...



- Total antimicrobial consumption in 2023 has increased since the decreases in 2020-2021
- "Access antibiotics"/penicillins are used to a large extent in Denmark in both sectors
- Elderly and children have the highest treatment frequency
- Treatment of urinary tract infections is decreasing, but still with considerable difference between elderly in their own homes and elderly at care homes
- Consumption at hospitals is increasing when measured by bed-days or admissions
- Product shortages still challenge supply of antibiotics, but action is taken on national and international level





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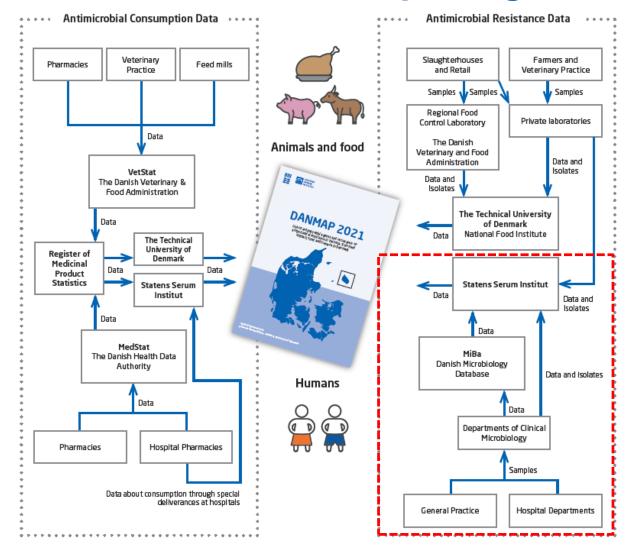
Antibiotic resistance in human clinical isolates

Mikkel Lindegaard & Ute Wolff Sönksen Referencelaboratoriet for antibiotikaresistens Statens Serum Institut



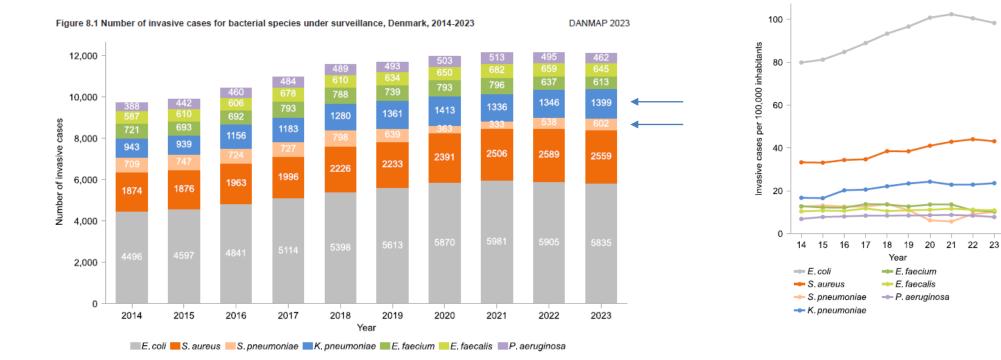


Resistance in human pathogens





Monitored invasive infections



E. coli - invasive infections and urine

Primary healthcare urines Invasive infections Hospital urines Denmark Denmark 50 7,000 Denmark 50 60,000 120,000 50 6,000 40 50,000 100,000 40 40 5,000 8 40,000 80,000 30 4.000 ច 30 30 60,000 30,000 ē 3,000 20 20 20 2,000 P 40,000 otal 20,000 🖪 10 10 20,000 10 10,000 1,000 0 0 n ٥ 0 15 16 17 18 19 20 21 22 23 14 14 15 16 17 18 19 20 21 22 23 14 15 16 17 18 19 20 21 22 23 Year Year Year -Trimethoprim (106164 in 2023) -Ampicillin (84398 in 2023) -3rd gen. cephalosporin (100171 in 2023) Ampicillin (5762 in 2023) Ciprofloxacin (5830 in 2023) - 3rd gen. cephalosporin (5426 in 2023)

Carbapenem (5212 in 2023)

Mecillinam (106203 in 2023)

Ciprofloxacin (83042 in 2023)

-Sulfonamide (93514 in 2023)

→ Piperacillin-tazobactam (5821 in 2023) → Cefuroxim (5820 in 2023)
→ Gentamicin (5828 in 2023)



Nitrofurantoin (91423 in 2023)

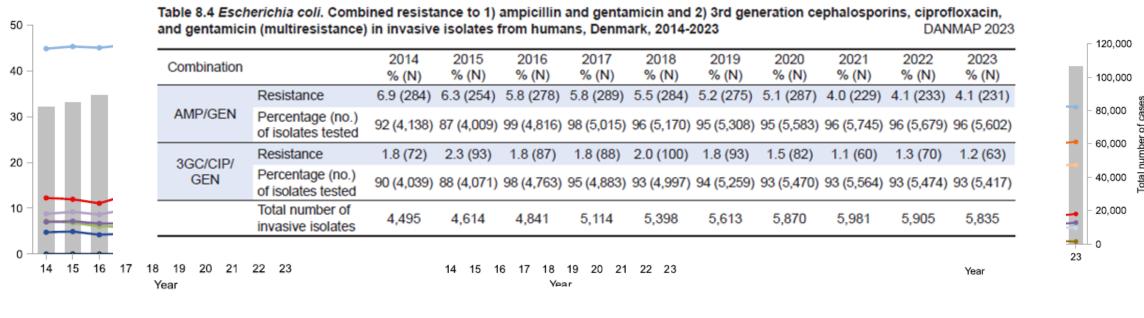


E. coli - invasive infections and urine

Invasive infections

Hospital urines

Primary healthcare urines



🛶 Ampicillin (5762 in 2023) 🛛 🔶 Ciprofloxacin (5830 in 2023) 🖛 3rd gen. cephalosporin (5426 in 2023)

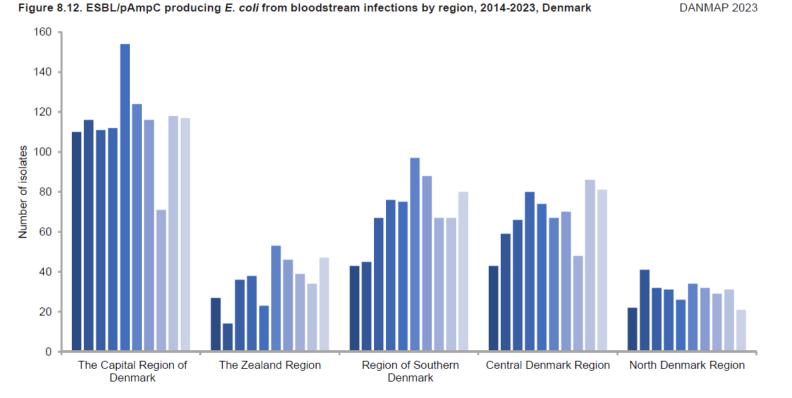
🛶 Piperacillin-tazobactam (5821 in 2023) 🐳 Cefuroxim (5820 in 2023) 🔷 Carbapenem (5212 in 2023)

--- Gentamicin (5828 in 2023)

Ampicillin (84398 in 2023)
 →3rd gen. cephalosporin (100171 in 2023)
 →Trimethoprim (106164 in 2023)
 →Sulfonamide (93514 in 2023)
 →Nitrofurantoin (91423 in 2023)
 →Ciprofloxacin (83042 in 2023)



ESBL E. coli from invasive infections



■2014 ■2015 ■2016 ■2017 ■2018 ■2019 ■2020 ■2021 ■2022 ■2023

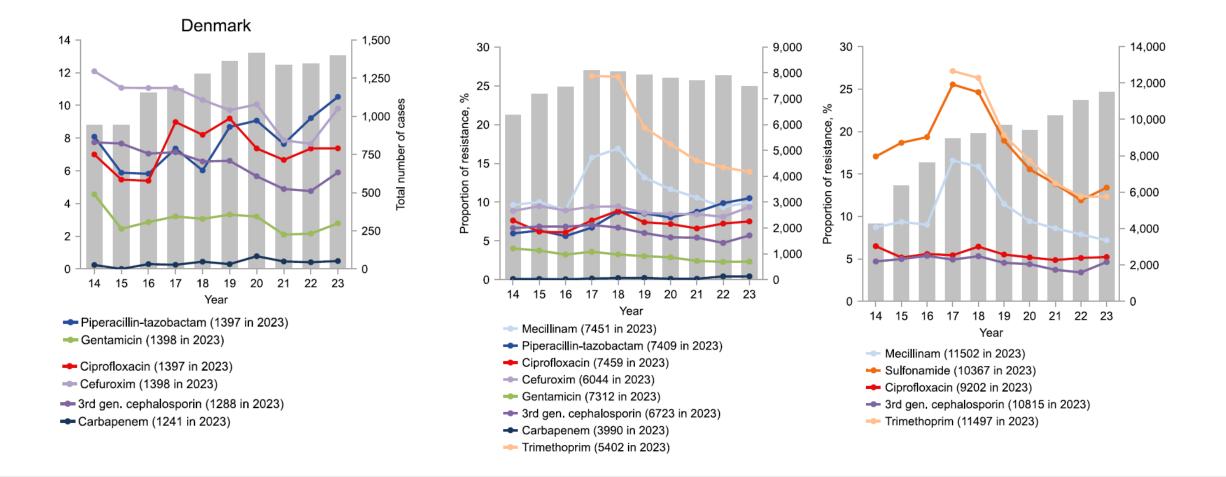


K. pneumoniae – invasive infections and urine

Invasive infections

Hospital urines

Primary healthcare urines





K. pneumoniae – invasive infections

Table 8.8 Invasive Klebsiella p	oneumoniae. T	able of res	sistance p	ercentage	s, 2014-202	23			DAN	IMAP 2023
Substance			Pe	rcent resist	ant invasiv	e K. pneun	<i>noniae</i> isola	ates		
Substance	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Piperacillin/tazobactam	8.1	5.9	5.8	7.4	6.1	8.7	9.1	7.5	9.2	10.5
Gentamicin	4.6	2.5	2.9	3.2	3.1	3.3	3.2	2.1	2.2	2.8
Ciprofloxacin	7.0	5.5	5.4	9.0	8.1	9.2	7.4	6.7	7.4	7.4
Cefuroxime	12.1	11.1	11.1	11.1	10.3	9.7	10.1	7.9	7.7	9.8
3rd gen. cephalosporins	7.7	7.7	7.3	7.1	6.1	6.6	5.3	4.9	4.8	5.9
Carbapenem	0.2	0.0	0.3	0.3	0.5	0.3	0.8	0.5	0.4	0.5
Total number of isolates	943	939	1,156	1,183	1,280	1,361	1,413	1,336	1,346	1,399

 Table 8.9 Invasive Klebsiella pneumoniae. Combined resistance to 3rd generation cephalosporins, ciprofloxacin, and gentamicin

 (multidrug-resistance) in invasive isolates from humans, Denmark, 2015-2023

 DANMAP 2023

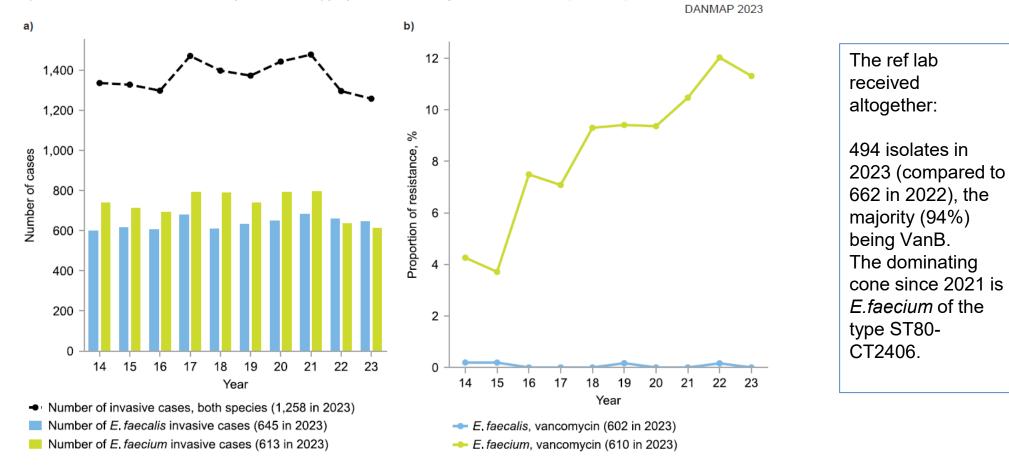
	2015	2016	2017	2018	2019	2020	2021	2022	2023
Resistance	% (N) 1.1 (9)	% (N) 1.6 (18)	% (N) 2.4 (27)	% (N) 1.7 (20)	% (N) 2.4 (30)	% (N) 1.5 (19)	% (N) 1.0 (13)	% (N) 1.0 (13)	% (N) 1.9 (24)
Percentage (no.) of isolates tested for combined resistance (multiresistance)	89 (840)	98 (1,131)	95 (1,122)	93 (1,188)	94 (1,275)	93 (1,308)	93 (1,248)	94 (1,259)	92 (1,287)
Total number of invasive isolates	943	1,156	1,183	1,280	1,361	1,413	1,336	1,346	1,399



Enterococci and vancomycin resistant enterocci

Figure 8.11 Invasive Enterococci faecalis/faecium isolates from humans:

a) annual number of isolates from unique cases and b) proportion of vancomycin resistant isolates, Denmark, 2014-2023



CPE

DANMAP 2023

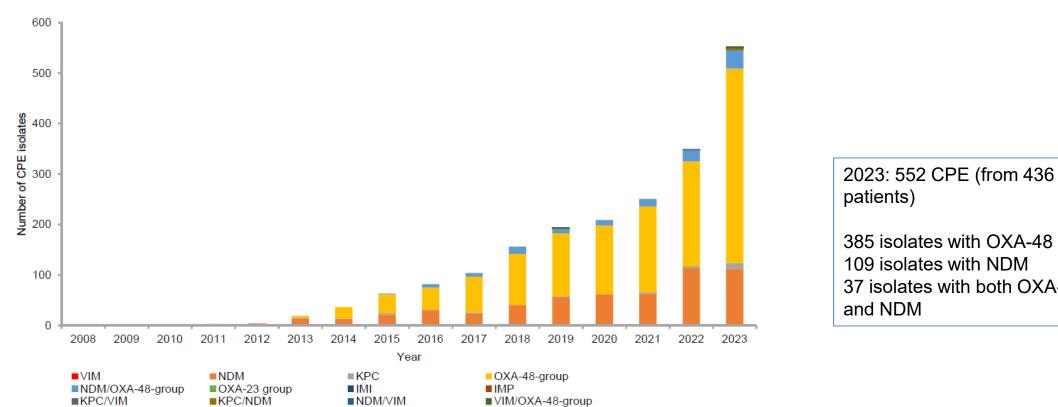


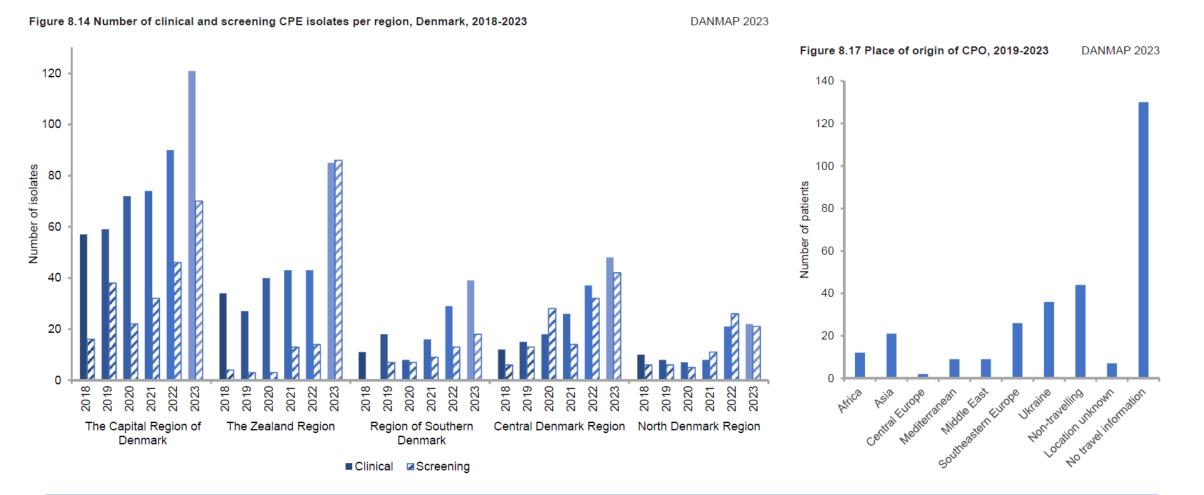
Figure 8.13 Numbers of carbapenemase-producing Enterobacterales (CPE), Denmark, 2008-2023

385 isolates with OXA-48 109 isolates with NDM 37 isolates with both OXA-48



CPE/CPO

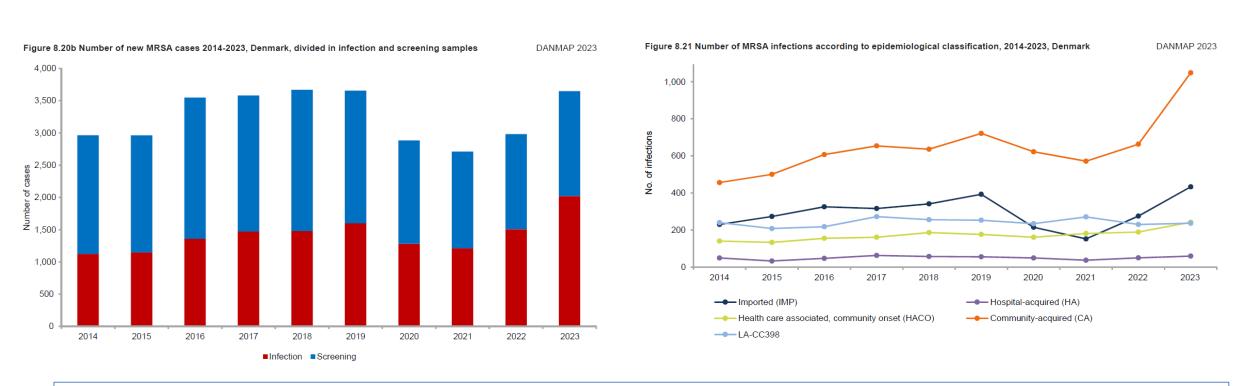
DANMAP



26 outbreaks in 2023, (24 CPE, 2 CPO): the majoriy domestic outbreaks, eight new, 18 "old" (known from previous years).

DANMAP





In 2023:

3,649 cases (20% increase) of MRSA compared to 2022 – primarily community-acquired or travel-related. LA-MRSA relatively stable, accounting for 23% of all MRSA infections.

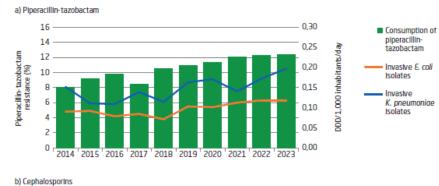
41 MRSA outbreaks (hospitals and nursing homes)

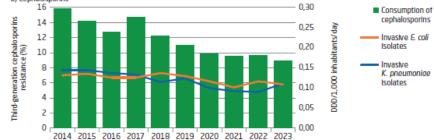
1.5% of bloodstream infections with S.aureus were caused by MRSA (39/2,571 cases)

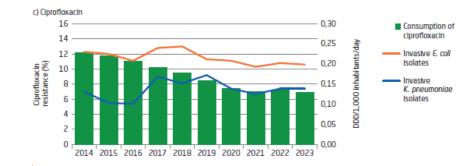
New in Summary

- comparisson of AMC and AMR for certain antibiotics

Figure 6.6 Resistance (%) in invasive Escherichia coli and Klebsiella pneumoniae combined with antimicrobial consumption (DID), Denmark, 2014-2023







Main messages

- The incidence of invasive infections appears to have reached a plateau
- After years of decreasing resistance rates, they have now either stabilised or are increasing
 - *K. pneumoniae* resistance towards piperacillin-tazobactam is now at 10.5 %!
- Decreasing numbers of invasive enterococcal infections but also in VRE a "real change" or less testing?
- Continued increase in outbreaks of CPO many with unknown epidemiology
- After a decrease in the number of MRSA during the pandemic, numbers are increasing again



This year's textboxes

Jeppe Boel

For further information: Jeppe Boel, jebl@ssi.dk

Textbox 8.1

Danish surveillance of azole resistant *Aspergillus fumigatus* from clinical samples - a 4-year update

Table 1 Yearly number of isolates and patients						Karen Marie Thyssen Astvad, Rasmus Krøger Hare, Karin Meinike Jørgensen, Nissrine Abou-Chakra, Jan Berg Gertsen Lise Kristensen, Flemming Schønning Rosenvinge, Lisbeth Lützen, Ea Sofie Marmolin, Bent Løwe Røder, Sofia Sulim, Michae									
				Qua	Pedersen, Jette Bangsborg, Raluca Datcu, Turid Snekloth Søndergaard and Maiken Cavling Arendrup										
	1 Q4 2018-Q3 2019		2 Q4 2019-Q3 2020				For further information: Karen Astvad, kaas@ssi.dk								
	N*	%	N	%	IN	%	IN	%	IN	%					
Patients	675		562		688		618		2,543						
Isolates	978		843		883		751		3,455						
Susceptible	922	94.3%	782	92.8%	832	94.2%	718	95.6%	3,254	94.2%					
Resistant	56	5.7%	61	7.2%	51	5.8%	33	4.4%	201	5.8%					
R env.	35	3.69													
R other Cyp51A	14	1.49													
R non-Cyp51A** 7 0.79		Textb	nx 8 2												
R env.: Resistance due to alterations of but were phenotypically similar to same- resistant isolate had an N248K mutation			Increasing rates of drug resistance in <i>Mycobacterium tuberculosis</i> isolates in Denmark												
Dorte Bek Folkvardsen and Erik Svensson, International Reference Laboratory of Mycobacteriology, S For further information: Dorte Bek Folkvardsen dbe@ssi.															
Textbox 8.3	lta fu			ve biel i				toving	in Ch	inclle					
First resu spp. in De				robial	resisi	lance	moni	toring	in Sh	igella					





DANMAP Seminar 2024

Antimicrobial consumption in animals

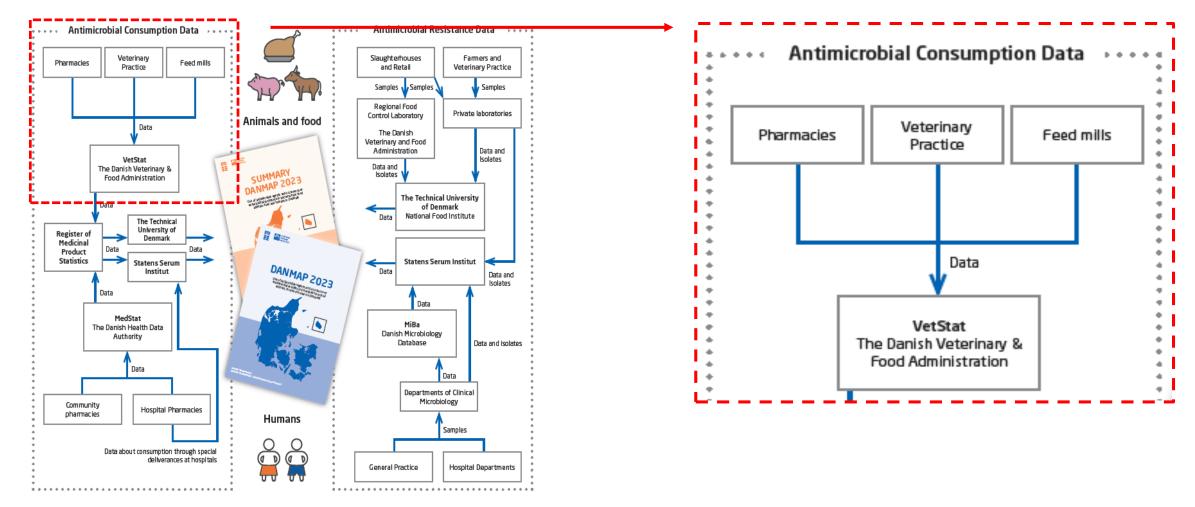


Marianne Sandberg Veterinarian, Senior researcher DTU, Food

Vibe Dalhoff Andersen Veterinarian, Senior researcher DTU, Food

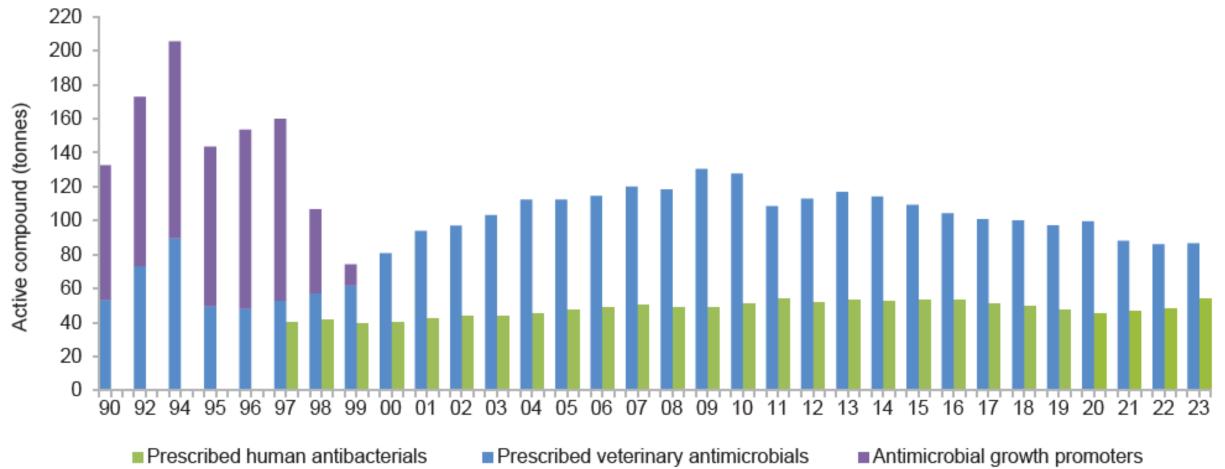


Data flow - VetStat



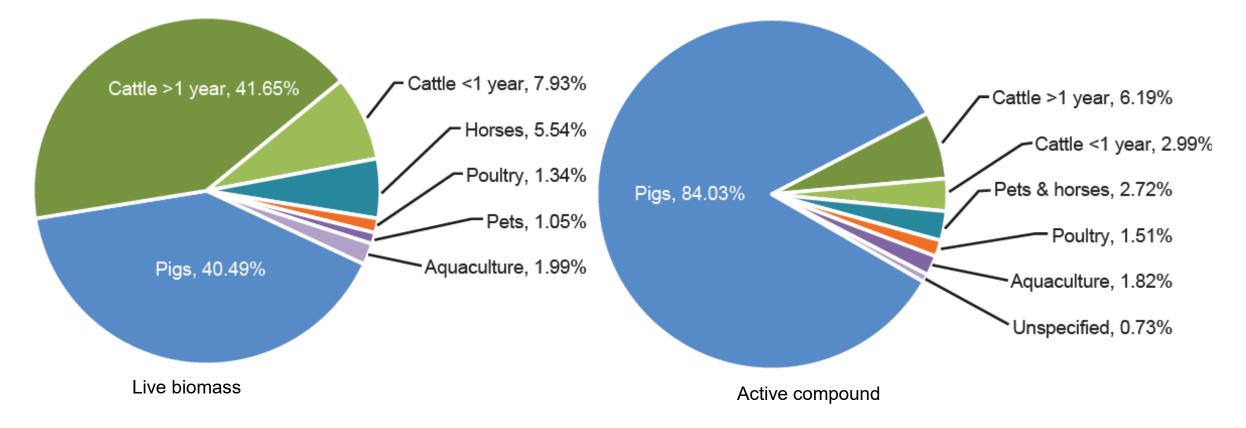


Antimicrobial consumption in animals and humans – a historical overview



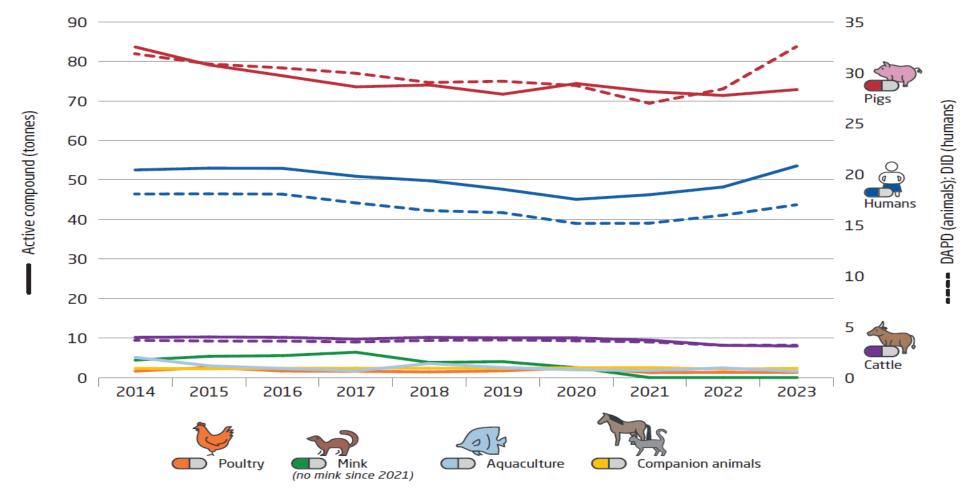


Relative distribution of biomass and antimicrobial consumption, animals, 2023





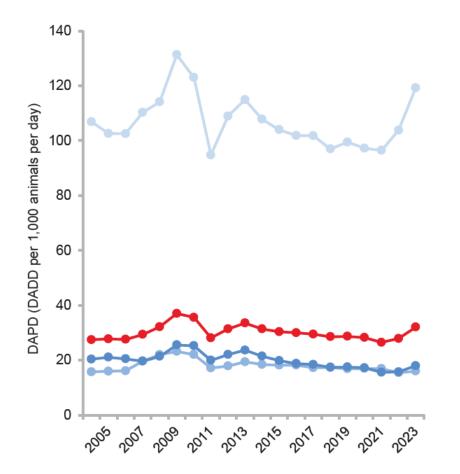
Antimicrobial consumption in animals and humans, 2014-2023

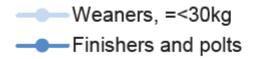


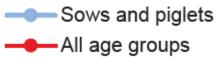
Small amounts of kg active compound were used by unspecified animal species in 2023



Consumption of antimicrobials in pigs

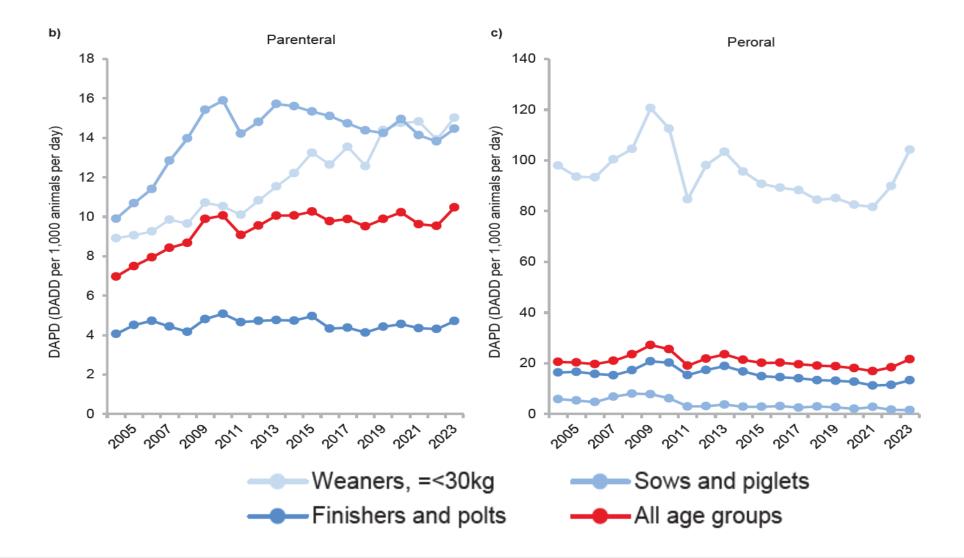






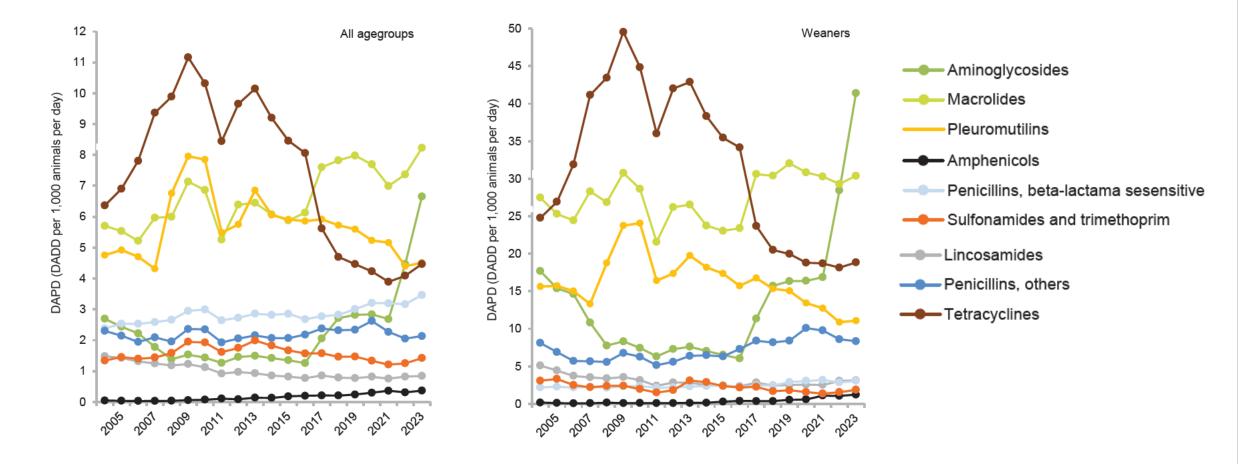


Consumption of antimicrobials in pigs



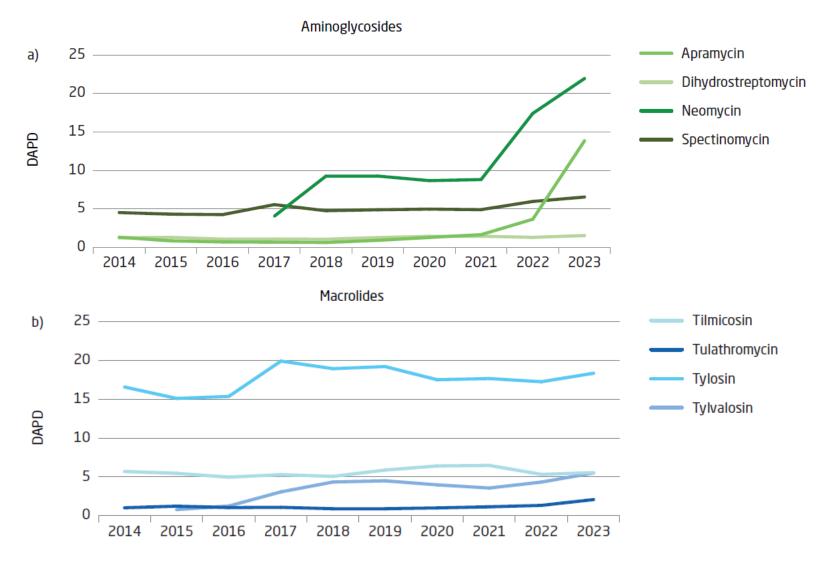


Consumption of antimicrobials in pigs



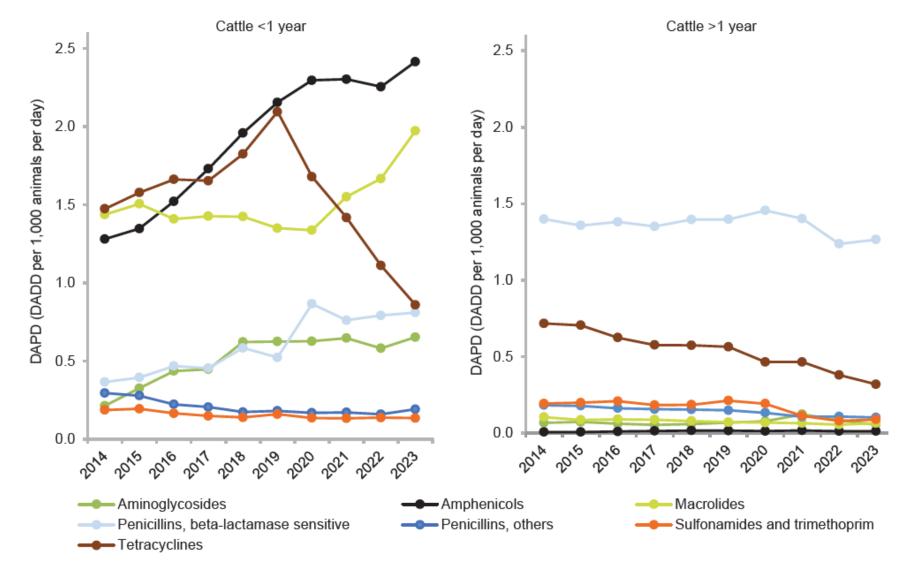


Consumption of antimicrobials in weaners



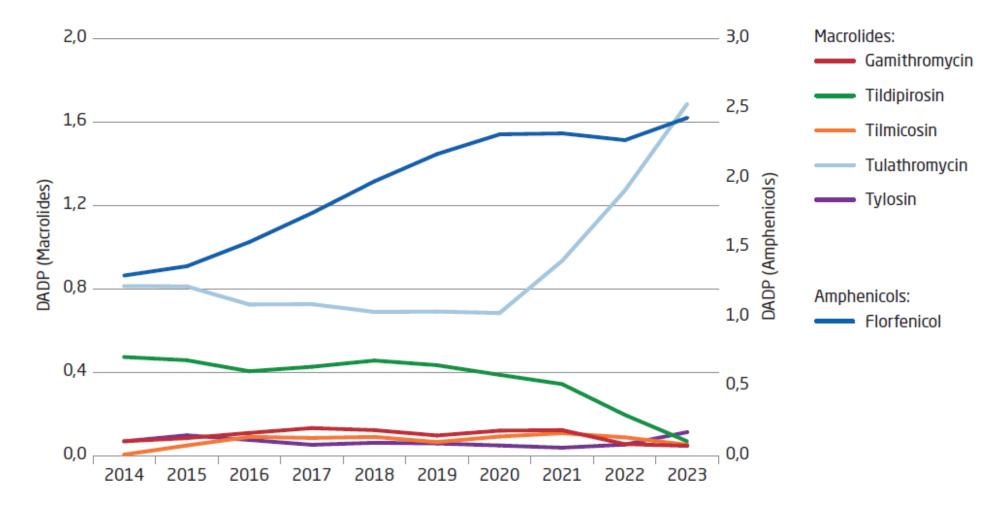


Consumption of antimicrobials in cattle



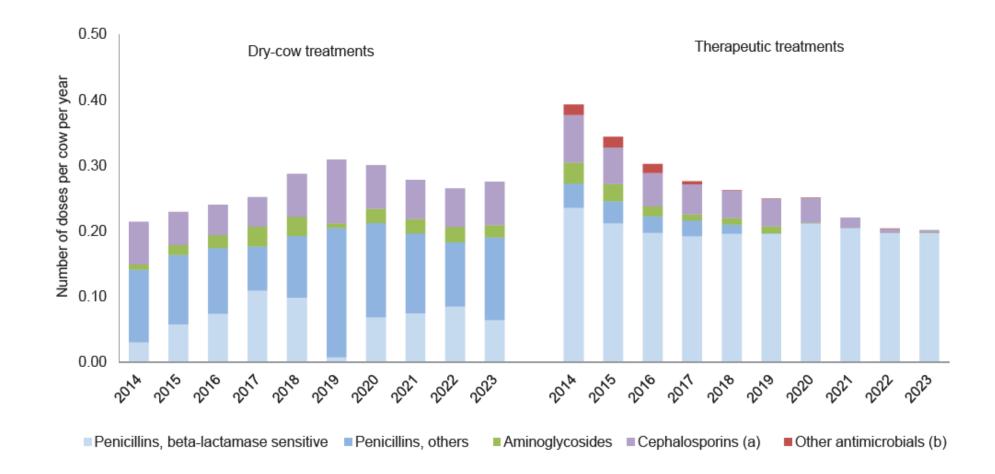


Consumption of antimicrobials in cattle < 1 year





Antimicrobial consumption in cattle, intramammaries





Text boxes

Textbox 4.1

A shift in the use of aminoglycosides following the ceased use of zinc oxide

The use of zinc oxide in Veterinary Medicinal Products (sideration of the risks for the environment. Prior to this, post-weaning diarrhea in piglets. The political ambition increase in antimicrobial use. While the Danish pig indus post-weaning diarrhea in the years leading up to the ba the use of neomycin in 2022; as described in the DANM

Textbox 4.2

Veterinary medicines and antibiotic resistance

In recent decades, veterinary medicine has focused on a One Health approach that integrates considerations regarding the health of both animals and humans. This has led to new guidelines for the responsible use of antibiotics in animals, aiming to reduce the development of resistance. As part of these efforts, the EU's Veterinary Medicines Regulation (2019/6) was implemented in 2022 with the goal of harmonizing the use of veterinary medicines, including reserving critical drugs for humans and generally ensuring responsible use. Veterinarians support these initiatives, but unfortunately, certain provisions in the regulation, especially Article 106, cause significant challenges for many veterinarians, which may impact a responsible use in a negative way. Veterinarians are required to prescribe medications strictly according to the Summary of Product Characteristics (SPC) which, depending on the available drugs, limits their ability to tailor treatments to individual animals or herds.





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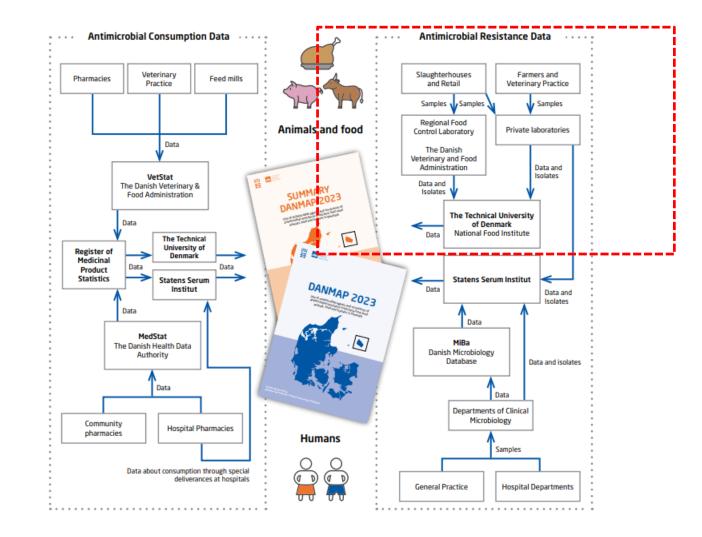
Antimicrobial resistance in indicator bacteria from food animals and food



Ana Sofia Ribeiro Duarte Senior Researcher, DVM, PhD

DTU National Food Institute





Overview of animal isolates reported in DANMAP 2023



Caecal samples:

- All samples: indicator *E. coli*
- Broilers and cattle: Campylobacter jejuni
- Pigs: Campylobacter coli, Salmonella spp. (S. Typhimurium, S. monophasic Typhimurium, S. Derby), Enterococcus faecalis

Pork 👙 | Pork 😸 Beef 블 | Beef Danish 😂 | Import 😂 | Danish 🗁 | Import 💬

- Cattle and pigs: ESBL/AmpC/CP-producing *E. coli*

Meat samples collected at retail:

- Pork and beef meat: ESBL/AmpC/carbapenemase-producing E. coli

EC Decision 2020/1729/EU

Carcass swabs at the slaughterhouse:



- Pig carcasses: Salmonella spp. (S. Typhimurium, S. monophasic Typhimurium, S. Derby)

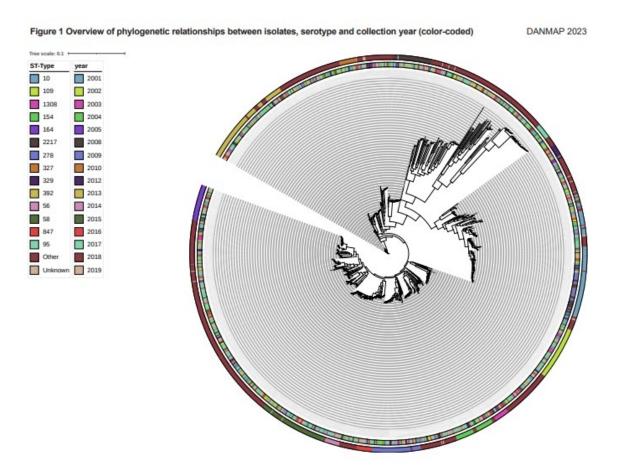
National Salmonella control program



Resistance in indicator bacteria - Textboxes

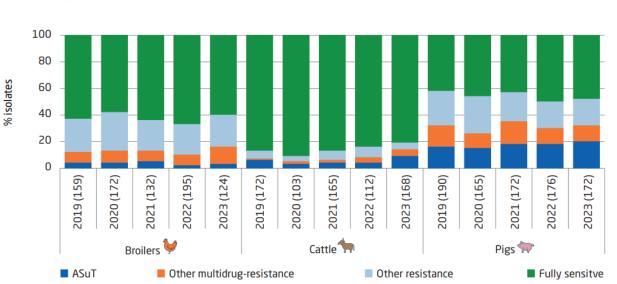
Textbox 7.1 – Ecogenomics of Danish cattle *E. coli* between 2001 and 2019

Saria Otani, Panos Sapountzi (DTU Food)

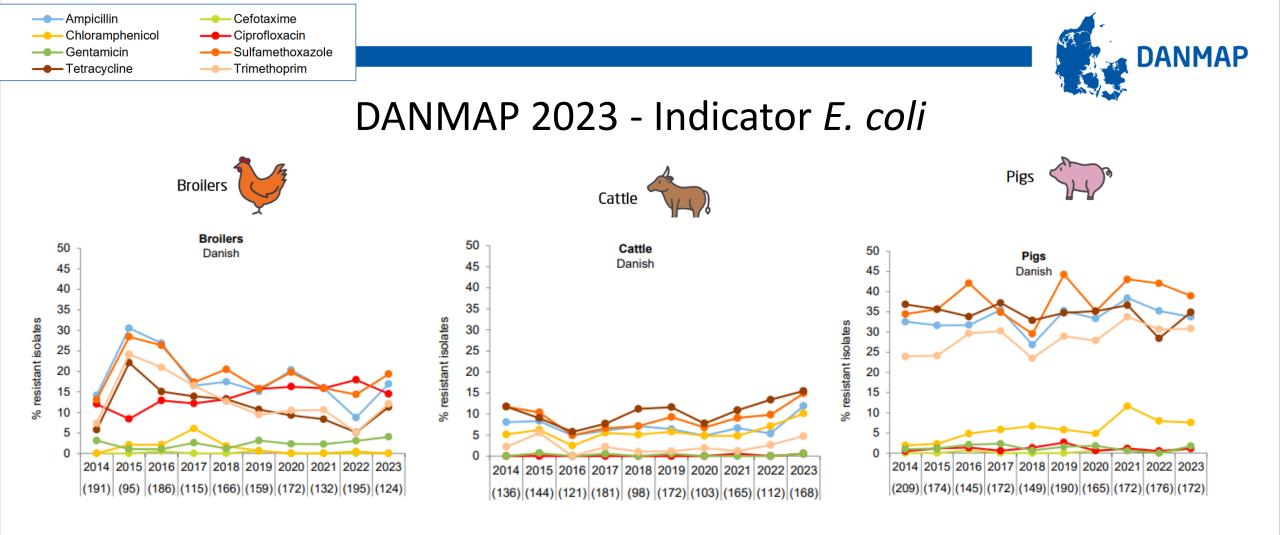




DANMAP 2023 - Indicator E. coli



- Figure 5.1 Distribution (%) of fully sensitive, resistant and multidrug-resistant *Escherichia coli* isolates from broilers, cattle and pigs, Denmark, 2019-2023
- In the last 5 monitoring years:
- No significant trend in %FS in broilers and pigs
- <u>Significant decrease in %FS in cattle</u>
- Significant increase in %MDR in cattle
- Ampicillin, Sulfamethoxazole and Tetracycline (ASuT) resistance still the <u>most common</u> MDR profile in cattle and pigs
- %ASuT increased in cattle
- Other AMR patterns dominate in broilers



- Increase in % resistance to <u>several substances</u> in **broilers** and continued increase in **cattle**
- Increase in % resistance to <u>tetracycline</u> in **pigs**

- Decrease in % resistance to <u>ciprofloxacin</u> in **broilers**
- Decrease in % resistance to <u>ampicillin</u> and

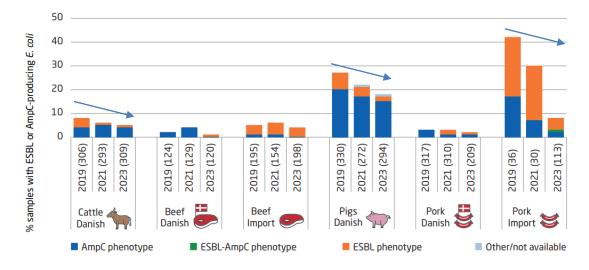
sulfamethoxazole in pigs



DANMAP 2023 - ESBL-, AmpC-, CP-producing E. coli

- No detection of **CP-producing** *E. coli*
- %ESBL/AmpC-producing E. coli:
- overall decreased in 2023
- 5-year significant decrease in cattle, pigs and imported pork
- higher in pigs than in cattle
- higher in imported meat

Figure 5.2 Occurrence (%) of samples with phenotypic ESBL- or AmpC-producing *E. coli* from animals and meat recovered by selective enrichment, Denmark, 2019-2023





DANMAP 2023 - ESBL-, AmpC- producing E. coli

Table 7.3 Number of ESBL and AmpC enzymes detected in beta-lactamase-producing *E. coli* isolates from animals and meat recovered by selective enrichment, Denmark, 2023 DANMAP 2023

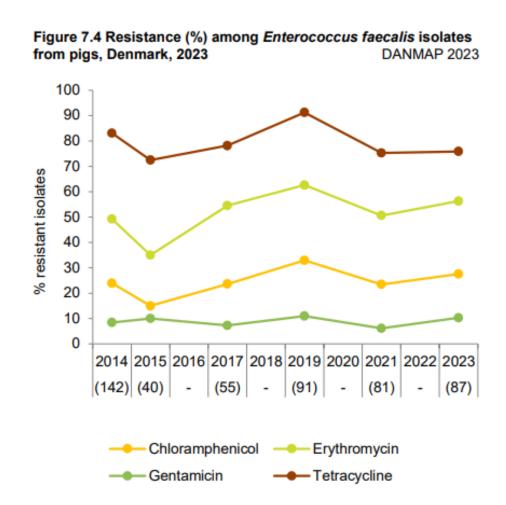
	Cattle	Bee	f	Pigs	P	Pork	
Enzymes	Danish	Danish	Import	Danish	Danish	Import	
blaCTX-M-1		1	1	5	3	2	
blaCTX-M-15	1		3			1	
blaCTX-M-27						1	
blaCTX-M-32			2				
blaCTX-M-55				2		3	
blaDHA-1	1			2			
blaOXA-1			1	1			
blaOXA-10	1						
blaSHV-12			1				
blaTEM-15	1						
blaTEM-52B	1						
Chromossomal AmpC (T-32A)				1			
Chromossomal AmpC (C-42T)	10		1	44	2	2	
Number of AmpC genotypes	9	0	1	44	2	2	
Number of ESBL genotypes	3	1	7	9	3	7	
Number of AmpC+ESBL genotypes	1	0	0	1	0	0	
Number (%) positive samples	13 (4%)	1 (1%)	8 (4%)	54 (18%)	5 (2%)	9 (8%)	
Number of tested samples	309	120	198	294	209	113	
Number of AmpC phenotypes	11	0		45	2	2	
Number of ESBL phenotypes	2	8		5	3	6	
Number of ESBL+AmpC phenotypes	0	0		1	0	1	
Other phenotypes	0	0		3	0	0	
Number of isolates (%)	13 (4%)	8 (4%)		54(18%)	5 (2%)	9 (8%)	
Number of samples	309	198		294	209	113	

- Phenotypic and genotypic profiles mostly in concordance
- 11 different ESBL genes detected
- Genes CTX-M-1 and CTX-M-15 most common among ESBL-producing isolates
- CTX-M-15 most frequent in isolates from imported beef
- Upregulated AmpC promotor C-42T mutations most common among AmpCproducing isolates, except for one T-32A mutation
- Two ESBL- and AmpC-producing isolates with C-42T mutation, together with blaOXA-1 (in pig) and blaOXA-10 (in cattle)



DANMAP 2023 - Indicator Enterococcus faecalis from pigs

- **No resistance** to ampicillin, ciprofloxacin, linezolid, teicoplanin, tigecycline and vancomycin
- **Overall increase** in resistance compared to 2021:
- 1% tetracycline
- 4% gentamicin
- 5% chloramphenicol and erythromycin
- 33% MDR, most common profile TET-ERY-CHL



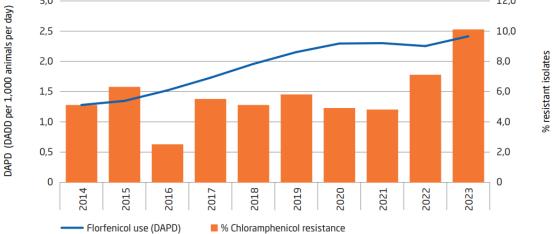


Trends of antimicrobial consumption and resistance in indicator E. coli from calves

10-year increase in the consumption of macrolides and amphenicols in calves

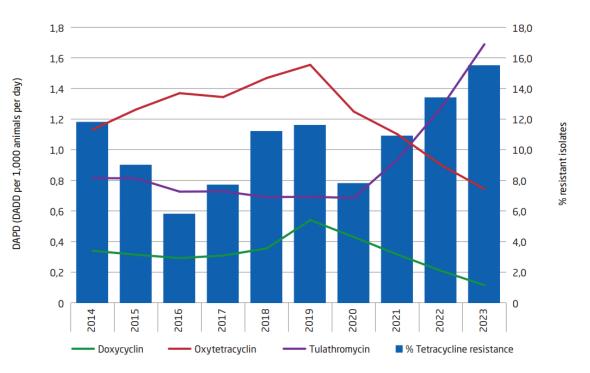


Figure 5.4 Amphenicol resistance (%) in indicator E. coli and florfenicol consumption (DAPD) in calves, Denmark, 2014-2023



increased use of florfenicol -> increase in chloramphenicol . resistance

Figure 5.5 Tetracycline resistance (%) in indicator E. coli and antimicrobial consumption (DAPD) in calves, Denmark, 2014-2023



increased use of tetracycline (until 2019) + increased use of ٠ tulathromycin (after 2019) -> increase in tetracycline resistance



DANMAP Explorer - interactive AMR data visualisation





DANMAP Explorer 1 Explore data on resistance in indicator and zoonotic bacteria

DANMAP Explorer 2 Explore data on ESBL/AmpCproducing *E. coli*

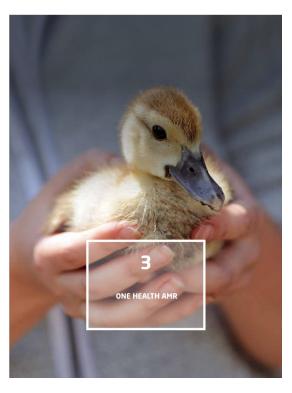
Available at : <u>www.danmap.org</u>





DANMAP Seminar 2024

One Health antimicrobial resistance

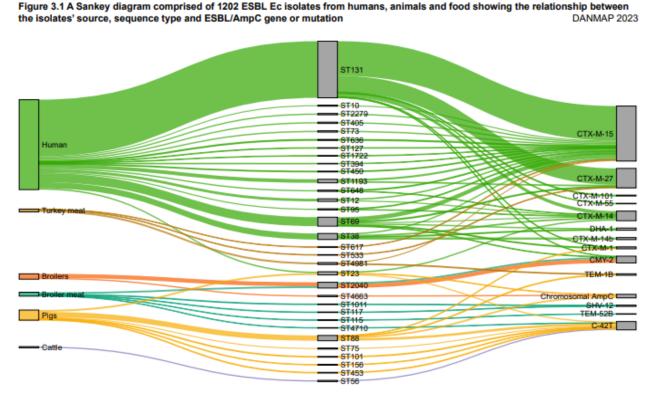


Ana Sofia R. Duarte, Patrick Munk DTU National Food Institute

Mikkel Lindegaard, Ute Wolff Sönksen Statens Serum Institut



DANMAP 2023 - ESBL-, AmpC- producing E. coli



The flows between nodes are coded according to source. Only flows of five or more isolates are shown

- Sequence types strongly associate with species:
- ST131 humans
- ST2040 broilers/broiler meat
- ST4981 turkey meat
- ST88 pigs
- ST56 for cattle
- Resistance determinants found in humans and animals/meat:
- AmpC plasmid-mediated gene CMY-2
- ESBL genes CTX-M-1, CTX-M-15 and CTX-M-27



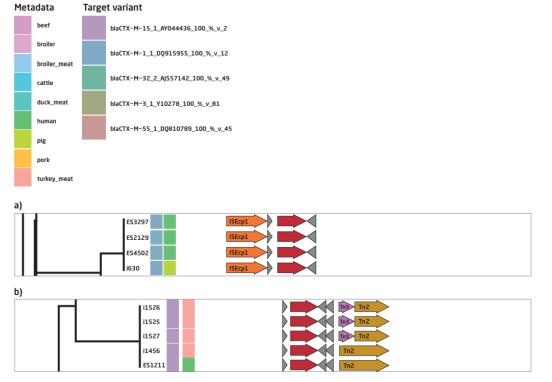
- CTX-M-15 and CTX-M-27 turkey meat
- CMY-2 broilers and broiler meat
- CTX-M-1 pigs

DANMAP 2023 - ESBL-, AmpC- producing E. coli

- Flankophile analysis of the DNA sequence of the gene's flanking region (*i.e.* the genetic code that comes before and after a gene)
- determination of a probable common source -> possibility of horizontal gene transfer
- Focus on ESBL genes CTX-M-1, CTX-M-14, CTXM-15, CTX-M-27, CTX-M-55, TEM-52B, and AmpC genes DHA-1, CMY-2

- CTX-M-1 could be shared by pigs and humans (a)
- CTX-M-15 could be shared by humans and turkey meat (b)

Figure 8.2 ESBL genes CTX-M-1 (a) and CTX-M-15 (b) identical in both gene and flanking region sequences between *E. coli* isolates of animal origin and human origin



Details from Flankophile plots, showing a – clustering of CTX-M-1 genes of human- and pig origin; b - clustering of CTX-M-15 genes of humanand turkey meat origin. From left to right: distance tree of the gene's flanking regions (straight vertical lines indicate that the flanking regions are 95% identical); color annotation columns representing the target variant (left) and the host (right); arrows depicting the gene synteny, with the target sequence in red





DANMAP Seminar 2024

Resistance in Zoonotic Bacteria



Ana Sofia R. Duarte (DTU Food) Jeppe Boel (SSI)

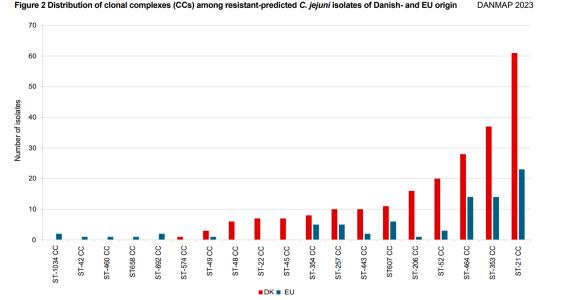
Joana Pessoa Postdoc, DVM, PhD

Foodborne Pathogens and Epidemiology DTU National Food Institute

Resistance in zoonotic bacteria - Textboxes

Textbox 6.1 – Trends in phenotypic- and genotypic fluoroquinolone resistance in *Campylobacter jejuni* from broilers and broiler meat in Denmark

Ana Sofia Ribeiro Duarte (DTU)



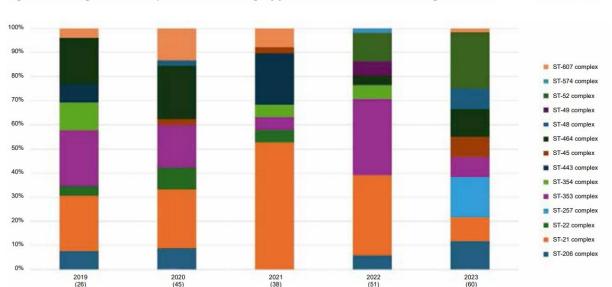


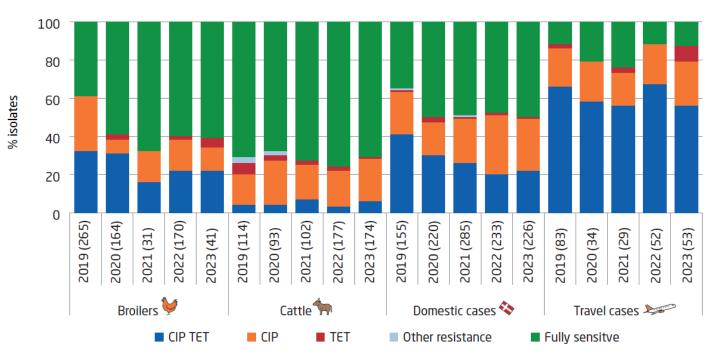
Figure 3 Percentage of clonal complex abundance among C. jejuni resistant mutants of Danish origin, 2019-2023







DANMAP 2023 – Campylobacter jejuni



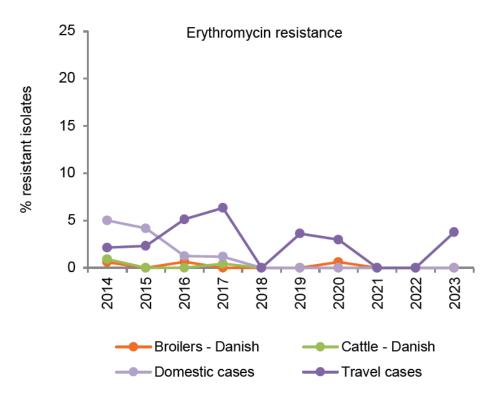
AMR profiles among *C. jejuni*

- Small increase in % FS in broilers
- Decrease in %FS in cattle
- Resistance levels among domestic
 cases comparable with 2022
- Overall highest resistance: travel cases
- CIP & TET resistance remains common in humans & animals

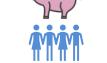


DANMAP 2023 – C. jejuni & C. coli

Resistance to macrolides & carbapenems remained low



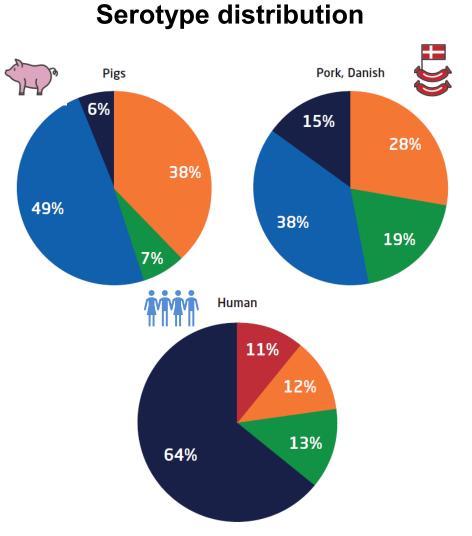
Campylobacter coli



- Reported for the 1st time for clinical human isolates
- Overall higher resistance levels in human isolates
- Erythromycin resistance at 6% & 11% in pigs & humans
- CIP & TET resistance increased in pigs
- No ertapenem resistance in pigs



DANMAP 2023 – Salmonella spp.

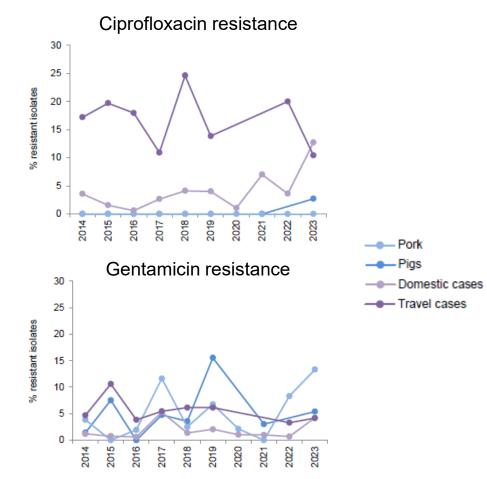


AMR profiles



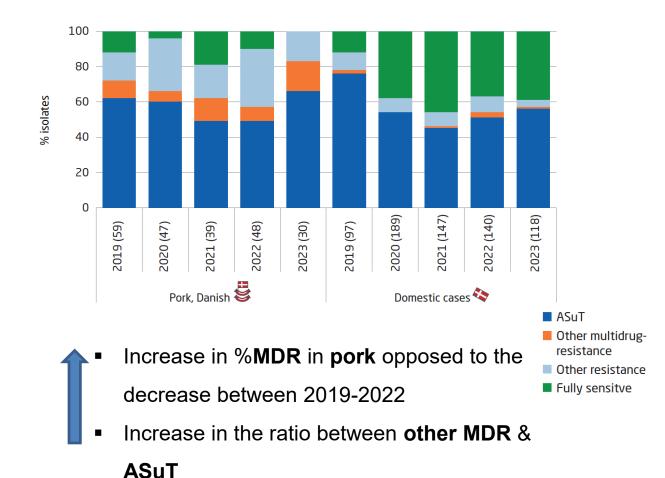


DANMAP 2023 – S. Typhimurium



- Increase in %CIP resistance in domestic cases
- Overall Increase in %gentamicin resistance

AMR profiles

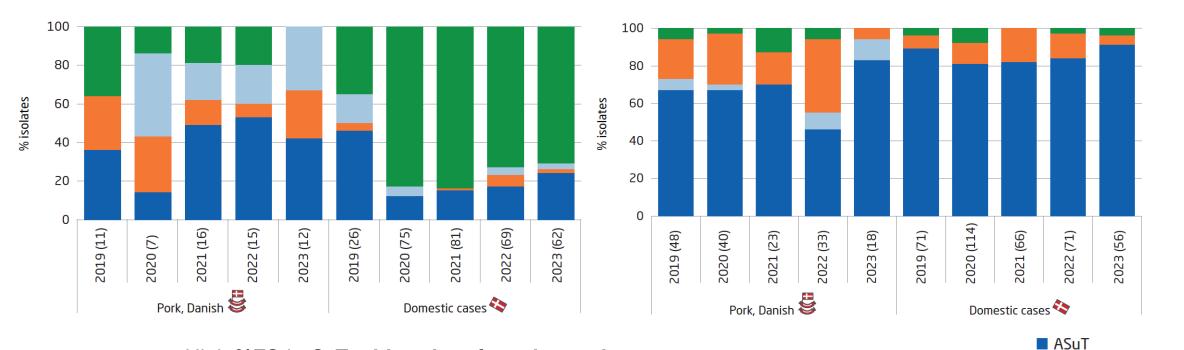




DANMAP 2023 – S. Typhimurium

S. Typhimurium

Monophasic S. Typhimurium



- High %FS in S. Typhimurium from domestic cases
- Markedly higher **%MDR** in **monophasic** S. Typhimurium
- Evident differences in %ASuT among S. Typhimurium & monophasic S. Typhimurium Fully sensitive

Other multidrugresistance

Other resistance



E

DANMAP 2023 – S. Enteritidis & S. Derby

S. Enteritidis

MM

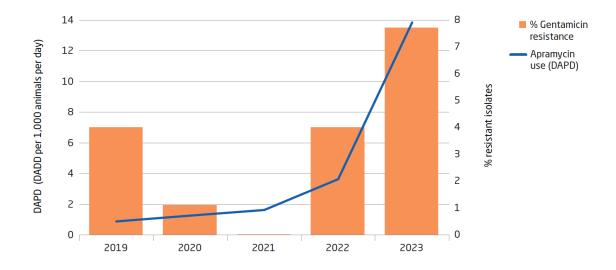
	Human					
	Domestically acquired	Travel abroad reported	Total			
Antimicrobial agent	%	%	%			
Amikacin	0	0	0			
Ampicillin	8	11	9			
Azithromycin	0	0	0			
Cefotaxime	0	0	0			
Ceftazidime	0	0	0			
Chloramphenicol	0	0	0			
Ciprofloxacin	47	32	39			
Colistin	42	32	37			
Gentamicin	0	0	0			
Meropenem	0	0	0			
Nalidixic acid	47	32	39			
Sulfonamide	5	0	3			
Tetracycline	3	5	4			
Tigecycline	5	3	4			
Trimethoprim	0	0	0			
Fully sensitive (%)	39	49	45			
Number of isolates	38	37	76			

- Chloramphenicol ----- Ampicillin ---------Gentamicin ---- Tetracycline ---- Trimethoprim

S. Derby

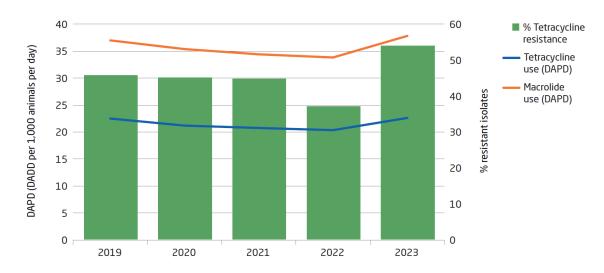


Gentamicin resistance & apramycin consumption (DAPD) in weaners



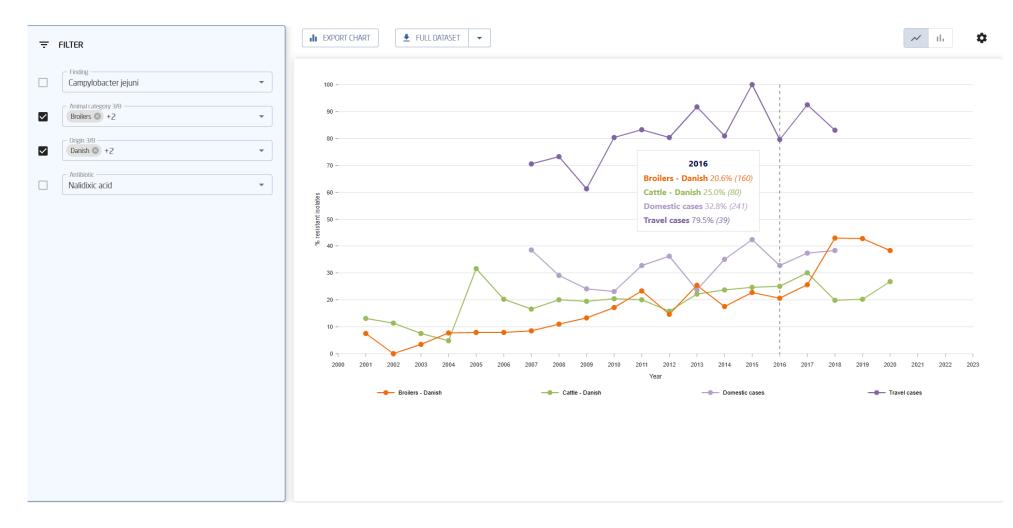
- Increase in the use of **apramycin**
- Increase in %gentamicin resistance

Tetracycline resistance & macrolide & tetracycline consumption (DAPD) in weaners & finishers



- Increase in the use of tetracyclines & macrolides
- Increase in %tetracycline resistance

DANMAP Explorer - interactive AMR data visualisation



Available at: www.danmap.org

DANMAP





Resistance in pathogenic bacteria from pigs

Lina M. Cavaco, Mikkel Lindegaard, Ute W. Sönksen, Pia T. Hansen & Jesper Larsen Bacteria, Parasites and Fungi Statens Serum Institut

Peter Damborg Department of Veterinary and Animal Sciences University of Copenhagen

Svend Haugegaard & Charlotte M. Salomonsen Veterinary Laboratory The Danish Agriculture and Food Council

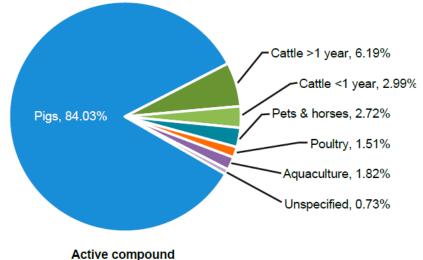


DANMAP

Background

Veterinary Laboratory, The Danish Agriculture and Food Council

- Receives clinical samples from pigs
- Performs bacterial culturing, species identification and antimicrobial susceptibility testing (AST)
- Published in **DANMAP** since 2015
 - Actinobacillus pleuropneumoniae
 - Lung infections
 - Haemolytic Escherichia coli
 - Primarily diarrhoea in weaners
 - Streptococcus suis
 - Septicaemia, meningitis, arthritis, endocarditis and other organs



DANMAP

Background

Danish Veterinary Consortium

- Whole-genome sequencing (WGS)
 - Illumina platforms
- Identification of resistance genes/mutations
 - ResFinder and PointFinder
- Comparison of AST and WGS results
 - 1st choice: ECOFFs (EUCAST)
 - 2nd choice: Tentative ECOFFs (EUCAST)
 - 3rd choice: Animal-specific clinical breakpoints (CLSI)
 - 4th choice: Human clinical breakpoints (CLSI)

List of pathogenic bacteria

- A. pleuropneumoniae (AST and WGS)
- Bordetella bronchiseptica (AST and WGS)
- Clostridium perfringens (WGS)
- Erysipelothrix rhusiopathiae (WGS)
- Haemolytic and non-haemolytic E. coli (AST and WGS)
- Glaesserella parasuis (WGS)
- Klebsiella pneumoniae (AST and WGS)
- Salmonella enterica (AST and WGS)
- Staphylococcus hyicus (AST and WGS)
- S. suis (AST and WGS)

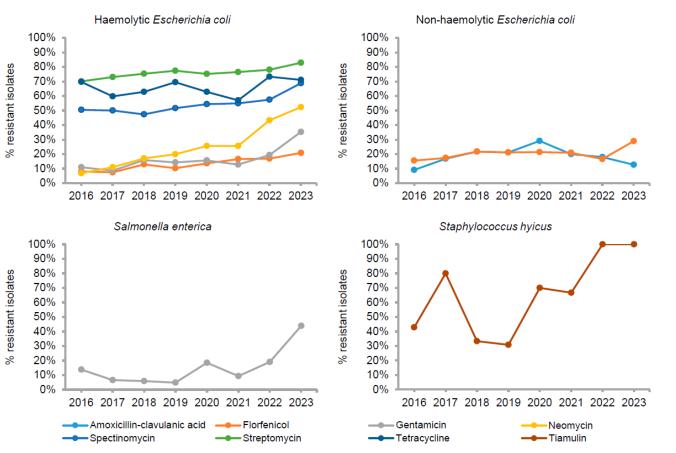


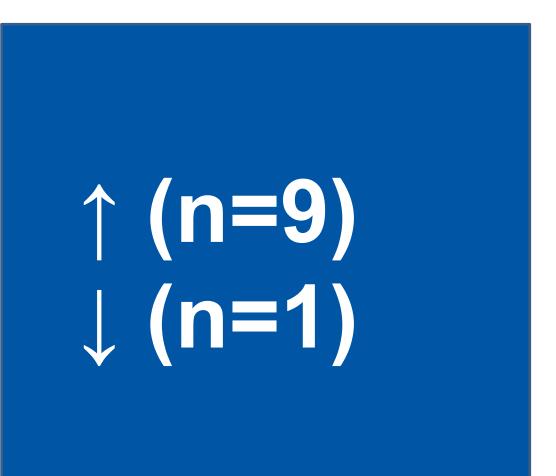
AST (phenotypic resistance)

 Figure 9.1 Statistically significant temporal changes in antimicrobial resistance phenotypes among pathogenic bacteria from pigs,

 Denmark, 2023 vs. 2022 and 2023 vs. 2018

 DANMAP 2023







WGS (resistance mechanisms)

Table 9.3 Statistically significant temporal changes in resistance mechanisms identified through whole genome sequencing of pathogenic bacteria from pigs, Denmark, 2023 vs. 2022 and 2023 vs. 2021 DANMAP 2023

Pathogen	Resistance	Class	Phenotype	2021	2022	2023	2023 vs. 2022	2023 vs. 2021
	gene/mutation			Presence (%)	Presence (%)	Presence (%)	P value	P value
Ср	ant(6)-lb	Aminoglycoside	Streptomycin	73.8%	85.7%	87.8%	0.80	0.03
	tet(44)	Tetracycline	Doxycycline, Tetracycline, Minocycline	73.8%	85.7%	87.8%	0.7989	0.0298
H-Ec	aac(3)-IV	Aminoglycoside	Apramycin, Gentamicin, Tobramycin	9.6%	21.8%	25.8%	0.5081	0.0037
	aph(3')-la	Aminoglycoside	Neomycin, Kanamycin, Lividomycin, Paromomycin, Ribostamycin	30.8%	34.5%	62.9%	0.0001	0.0000
	tet(B)	Tetracycline	Doxycycline, Tetracycline, Minocycline	21.2%	35.5%	38.2%	0.7677	0.0110
	aph(4)-la	Aminoglycoside	Hygromycin	9.6%	20.0%	21.3%	0.8611	0.0269
	bla _{TEM-127}	Beta-lactam	Amoxicillin, Ampicillin, Cephalothin, Piperacillin, Ticarcillin	0.0%	0.9%	4.5%	0.1749	0.0436
	cmIA1	Amphenicol	Chloramphenicol	14.4%	7.3%	18.0%	0.0279	0.5580
	mef(C)	Macrolide	Erythromycin	0.0%	0.0%	4.5%	0.0385	0.0436
	mph(G)	Macrolide	Erythromycin	0.0%	0.0%	4.5%	0.0385	0.0436
	tet(B)	Tetracycline	Doxycycline, Tetracycline, Minocycline	21.2%	35.5%	38.2%	0.7677	0.0110
NH-Ec	floR	Amphenicol	Chloramphenicol, Florfenicol	22.8%	11.5%	28.6%	0.0264	0.4669
	Inu(F)	Lincosamide	Lincomycin	5.4%	0.0%	8.6%	0.0375	0.5334
	mef(C)	Macrolide	Erythromycin	3.3%	1.9%	12.9%	0.0426	0.0315
	mph(B)	Macrolide	Erythromycin, Spiramycin, Telithromycin	8.7%	7.7%	0.0%	0.0308	0.0104
	mph(G)	Macrolide	Erythromycin	3.3%	1.9%	12.9%	0.0426	0.0315
Кр	aph(3")-lb	Aminoglycoside	Streptomycin	8.3%	37.5%	54.2%	0.3487	0.0111
	aph(6)-ld	Aminoglycoside	Streptomycin	8.3%	37.5%	54.2%	0.3487	0.0111
Se	aac(3)-IV	Aminoglycoside	Apramycin, Gentamicin, Tobramycin	0.0%	7.7%	25.8%	0.0509	0.0177
	aph(4)-la	Aminoglycoside	Hygromycin	0.0%	7.7%	25.8%	0.0509	0.0177
	bla _{тем-18}	Beta-lactam	Amoxicillin, Ampicillin, Cephalothin, Piperacillin, Ticarcillin	63.2%	59.0%	87.1%	0.0155	0.0776
	sul1	Folate pathway antagonist	Sulfamethoxazole	31.6%	20.5%	51.6%	0.0107	0.2420
	tet(B)	Tetracycline	Doxycycline, Tetracycline, Minocycline	47.4%	59.0%	77.4%	0.1285	0.0371
Ss	erm(B)	Macrolide, Lincosamide, Streptogramin B	Erythromycin, Lincomycin, Clindamycin, Quinupristin, Pristinamycin IA, Virginiamycin S	58.3%	64.8%	74.3%	0.1272	0.0201

Abbreviations: Cp, Clostridium perfringens; H-Ec, haemolytic Escherichia coli; NH-Ec, non-haemolytic Escherichia coli; Kp, Klebsiella pneumoniae; Se, Salmonella enterica; Ss, Streptococcus suis

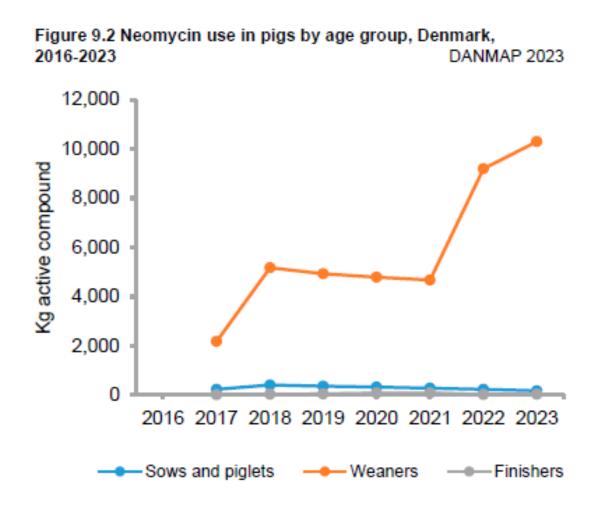


Neomycin resistance in haemolytic *E. coli* increased from 6.9% in 2016 to 52.3% in 2023

Problematic because neomycin is one of only a few drugs recommended in Denmark as first choice for treating *E. coli*-associated post-weaning diarrhoea



- aph(3')-la was present in 62.9% of sequenced haemolytic E. coli isolates
 - Also found in non-haemolytic *E. coli* (14.3%), *K. pneumoniae* (8.3%) and *S. enterica* (38.7%)
- Haemolytic *E. coli* also displayed medium to high frequencies of resistance to the other first-choice drugs
 - Amoxicillin/clavulanic acid (14.1%)
 - Spectinomycin (68.8%)
 - Trimethoprim/sulfamethoxazol (58.4%)
 - Streptomycin (82.9%)





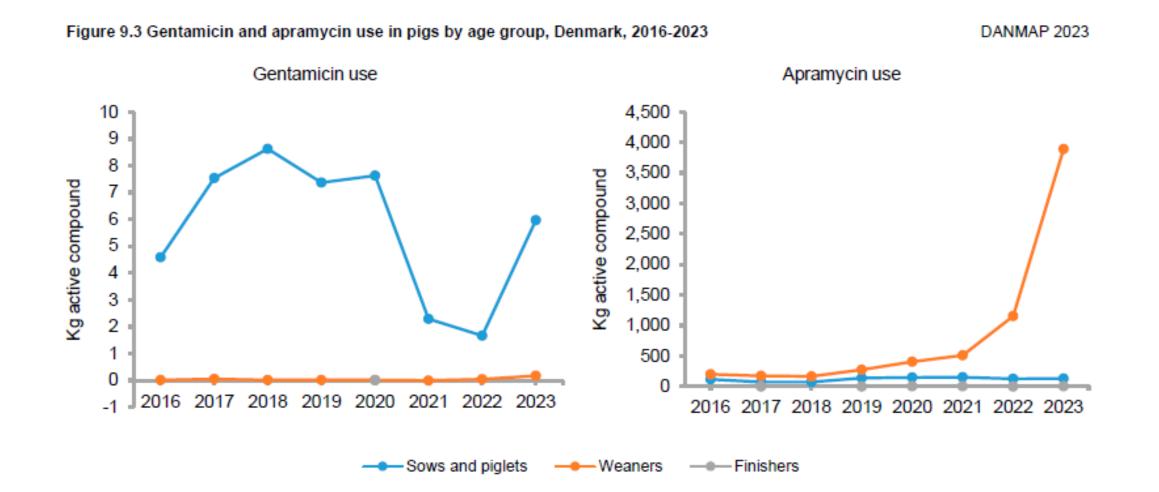
Gentamicin resistance in haemolytic *E. coli* increased from 10.9% in 2016 to 35.2% in 2023

Concerning because gentamicin is considered critically important for human medicine WHO



- *aac(3)-IV* was present in 25.8% of sequenced haemolytic *E. coli* isolates
 - Also found in non-haemolytic *E. coli* (7.1%),
 K. pneumoniae (12.5%) and *S. enterica* (25.8%)
- aac(3)-IId, aac(3)-IVa and ant(2['])-Ia were present in 6.7%, 1.1% and 2.2% of sequenced haemolytic *E. coli* isolates
- aac(3)-IV, aac(3)-IId and aac(3)-IVa confer resistance both to gentamicin and apramycin (but not to neomycin)







Gentamicin resistance in haemolytic *E. coli* increased from 10.9% in 2016 to 35.2% in 2023

Concerning because gentamicin is considered critically important for human medicine by WHO

... and because apramycin is recommended in Denmark as an alternative drug for treating *E*. *coli*-associated post-weaning diarrhoea

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Other findings

- Resistance towards carbapenems, 3rd, 4th and 5th generation cephalosporins, oxazolidinones and polymyxins remained at a low level
- The observed concordance between AST results and WGS-based detection of resistance mechanisms was
 - 99.6% for *A. pleuropneumoniae*
 - 79.6% for *B. bronchiseptica*
 - 94.2% for haemolytic E. coli
 - 94.3% for non-haemolytic E. coli
 - 76.0% for K. pneumoniae
 - 97.3% for S. enterica
 - 91.5% for S. hyicus
 - 94.5% for S. suis



DANMAP 2024

- Pathogenic bacteria from pigs

 AST but not WGS
- Bacteria causing acute mastitis in cows
 - Diagnostics at SSI
 - AST of selected pathogenic bacteria





Thank you for your attention!

Questions and comments



DANMAP

Thanks to



- Ana Sofia Ribeiro Duarte
- Anette M. Hammerum
- Anja Bjarnum
- Anne Kjerulf
- Asja Kunøe
- Brian Kristensen
- Charlotte M. Salomonsen
- Frank Hansen
- Hans-Christian Slotved
- Henrik Hasman
- Jeppe Boel
- Jesper Larsen
- Joana Pessoa
- Kasper Thystrup Karstensen
- Kurt Fuursted
- Lina M. Cavaco
- Lone Jannok Porsbo
- Louise Roer
- Majda Attauabi
- Marianne Sandberg
- Mikkel Lindegaard
- Patrick Munk
- Peter Damborg
- Pia T. Hansen
- Steen Hoffmann
- Svend Haugegaard
- Tinna Urth
- Ute Wolff Sönksen
- Vibe Dalhoff Andersen

- All Danish hospital pharmacies
- All data providers for textboxes and textbox authors
- Data Integration and Analysis Secretariat at SSI
- Infectious Disease Epidemiology & Prevention Unit at SSI
- National Food Institute, DTU
- Statistics Denmark
- The Danish Agriculture and Food Council
- The Danish Aquaculture Producer Organisation
- The Danish Health Data Authority and the Register of Medicinal Products Statistics
- The Danish Veterinary and Food Administration's Animal Medicine and Veterinary Trade Division
- The Danish Veterinary and Food Administration's Food and Feed Safety Division
- The Departments of Clinical Microbiology and the DANRES group - Danish Study Group for Antimicrobial Resistance Surveillance
- The meat inspection staff and company personnel at the participating slaughterhouses
- Unit of Mycology at SSI
- Local Veterinary and Food inspections units
- Antimicrobial Resistance Reference Laboratory and Surveillance
 Unit
- The Danish Veterinary and Food Administration's Laboratory, Ringsted
- Foodborne Pathogens Unit at SSI
- Neisseria and Streptococcus Typing Unit at SSI
- Staphylococcus Laboratory at SSI



EAAD – European Antibiotic Awareness Day



Antimicrobial resistance targets ⁱ -2024 update ⁱⁱ - (2023 data)							
European Union							
Reduce by 20% the total	2019 baseline	19.9	-				
consumption of antibiotics in humans	2023	20.0	+0.6%				
Defined daily doses (DDDs) per 1 000 inhabitants per day	2030 TARGET	15.9	-20%				
At least 65% of the total consumption of antibiotics in humans belongs to the	2019 baseline	61.1%	-				
Access' group of antibiotics As defined in the AWaRe classification of the WH0	2023	61.5%	+0.4% *				
*Percentage point difference from 2019.	2030 TARGET	65%	+3.9% *				
Reduce by 15% the total incidence of bloodstream infections with meticillin-	2019 baseline	5.6	-				
resistant <i>Staphylococcus aureus</i> (MRSA)*	2023	4.6	-17.6%				
Number per 100 000 population *Excluding France	2030 TARGET	4.8	-15%				
Reduce by 10% the total incidence of bloodstream infections with third-	2019 baseline	10.7	-				
generation cephalosporin-resistant <i>Escherichia coli*</i>	2023	10.4	-3.6%				
Number per 100 000 population uding France	2030 TARGET	9.7	-10%				
Reduce by 5% the total incidence of bloodstream infections with	2019 baseline	2.5	-				
carbapenem-resistant <i>Klebsiella pneumoniae*</i>	2023	4.0	+57.5%				
Number per 100 000 population	2030 TARGET	2.4	-5%				
 Council Recommendation targets on stepping up EU actions to combat antimicrobial resistance in a One Health approach Full data available in ECIC Annual Exidemicioaical Records on antimicrobial resistance and antimicrobial consumption 	h (2023/C 220/01)						



Read more at:



STATENSDANMAPSERUMThe Danish Integrated Antimicrobial ResistanceINSTITUTMonitoring and Research Programme

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DANMAP

DANMAP is the Danish Programme for surveillance of antimicrobial consumption and resistance in bacteria from food animals, food and humans.

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