



Antimicrobial use and resistance in food animals

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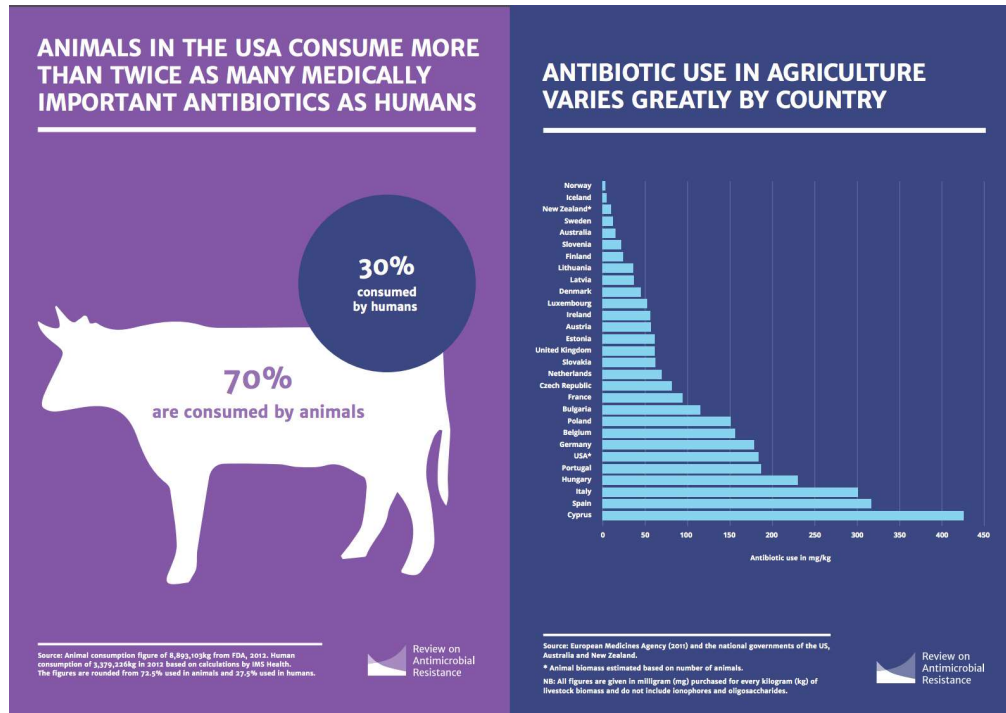
Prof. Veterinary Bacteriology, Royal Veterinary College

Lecture outline

- **Antimicrobial use in food animals**
 - Europe vs Denmark
 - Pigs vs cattle vs poultry
- **Antimicrobial resistance (AMR) in food animals**
 - Resistant bacteria of clinical interest (other than MRSA)
 - *Campylobacter*
 - *Salmonella*
 - ESBL-producing *Escherichia coli*
- Take-home messages

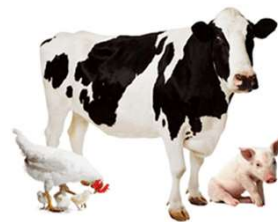
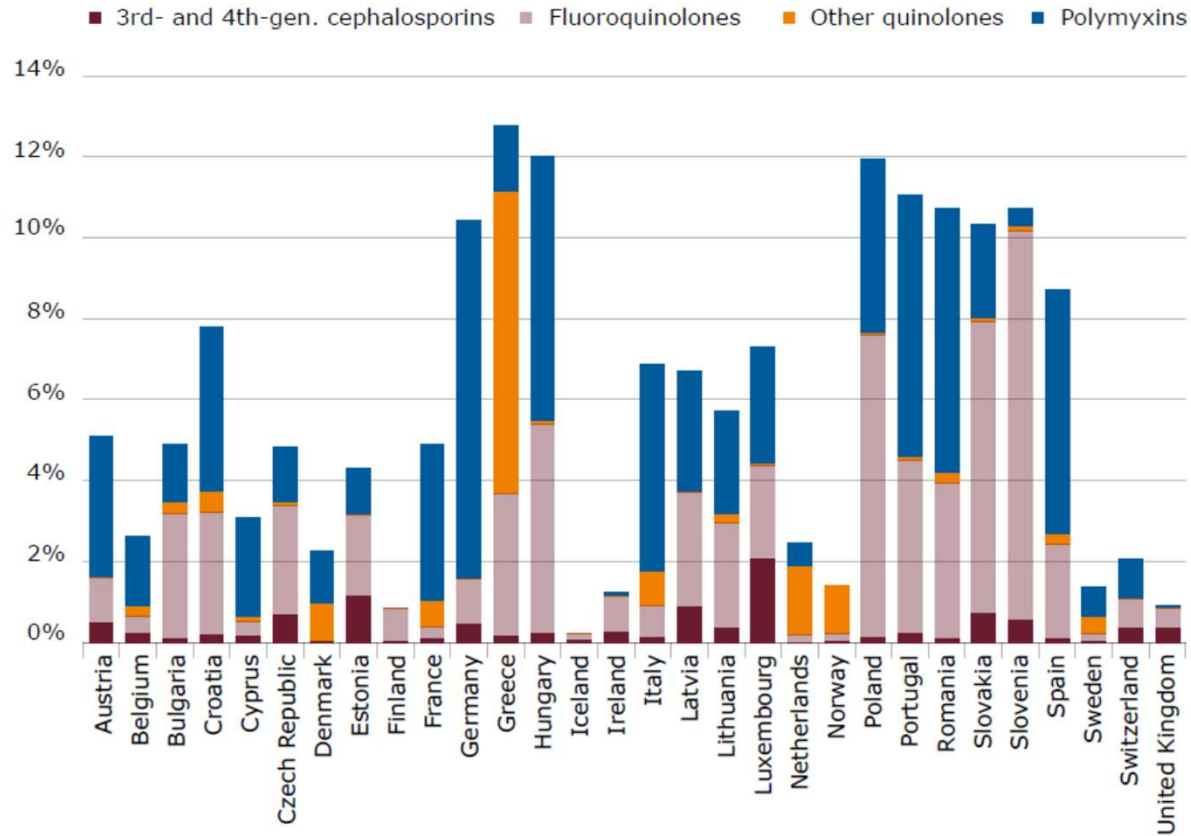


Antimicrobial use in food animals



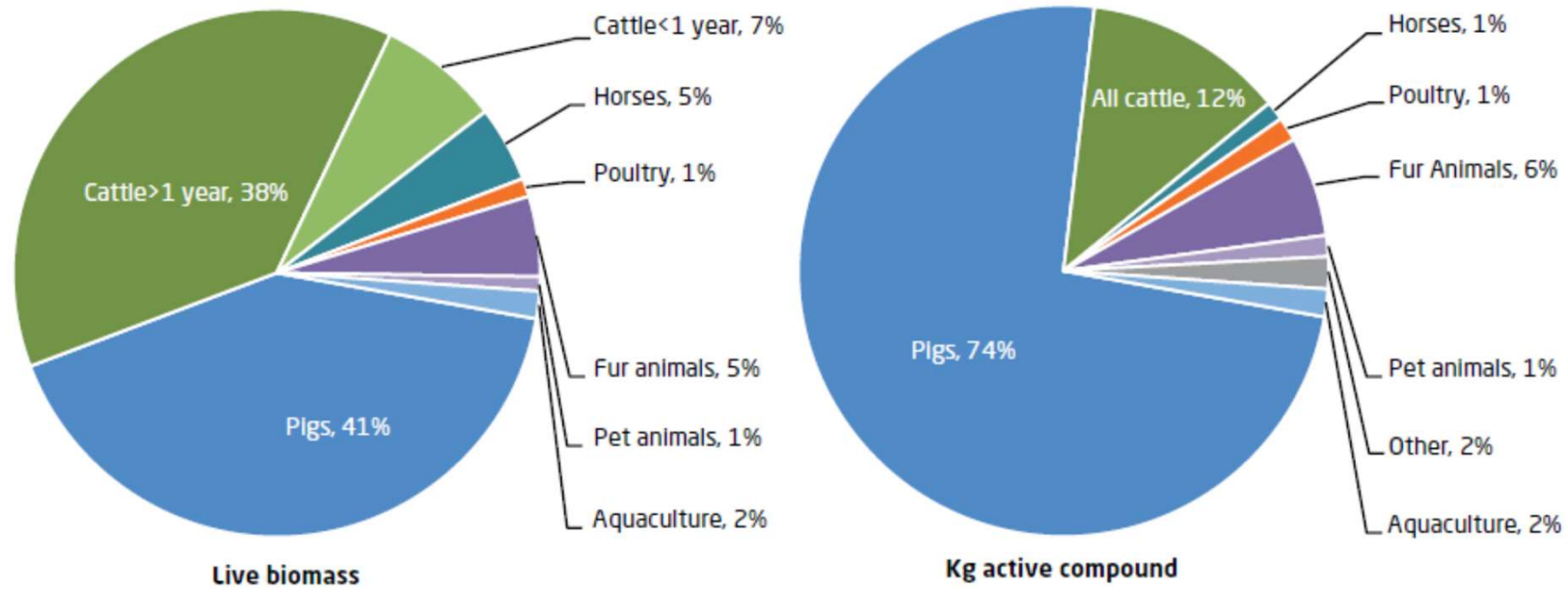
Consumption of CIAs in the EU

ESVAC report 2016 (www.ema.europa.eu)



Antimicrobial use in food animals in Denmark

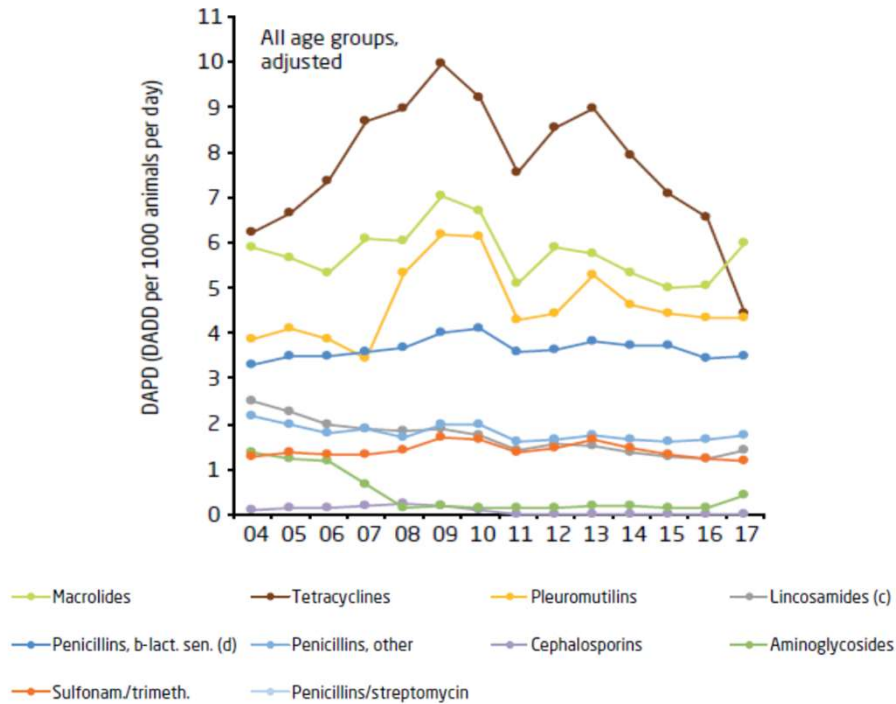
Live biomass and antimicrobial consumption per species
DANMAP 2017 (www.danmap.org)



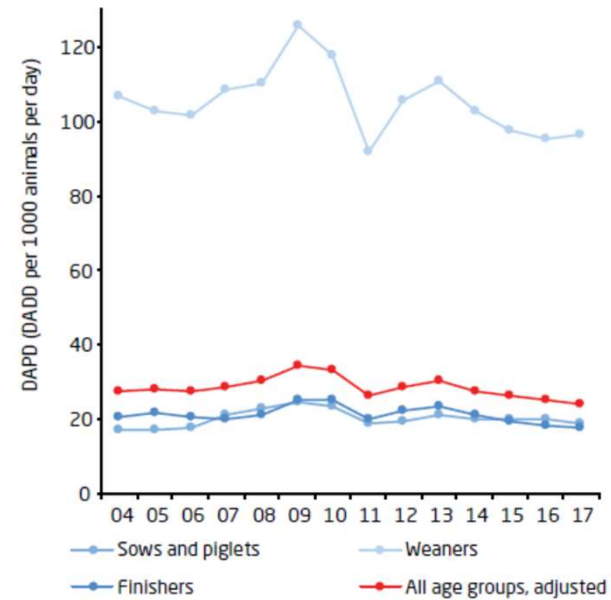
Antimicrobial use in pigs Denmark

DANMAP 2017 (www.danmap.org)

Per antibiotic class



Per age group



Use of colistin and zinc in pigs Denmark

DANMAP 2017 (www.danmap.org)

Figure 4.7 Total use of colistin in production animals, Denmark

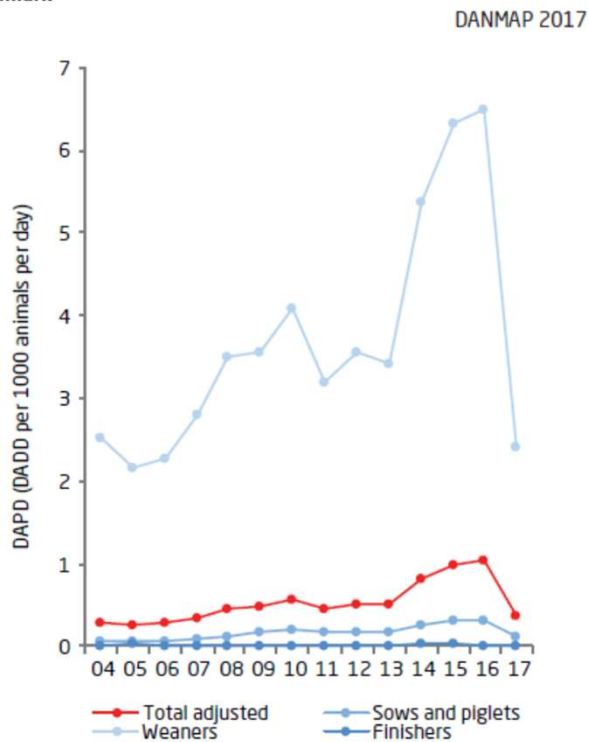
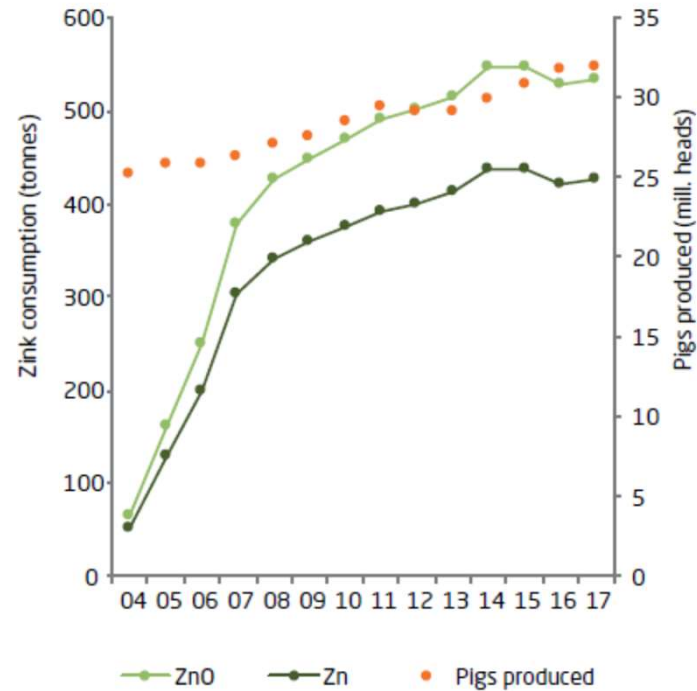


Figure 4.6 Consumption (tonnes) of zinc oxide (ZnO) and zinc (Zn) in the pig production, Denmark DANMAP 2017



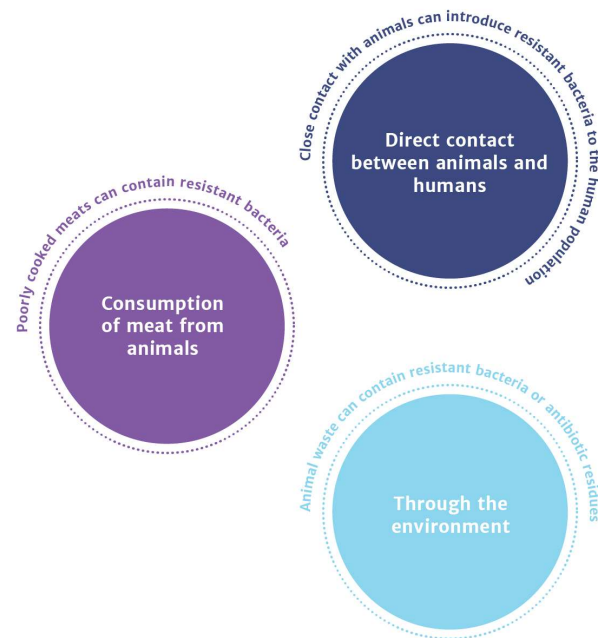
Consumption of colistin in the EU

ESVAC report 2016 (www.ema.europa.eu)



Antimicrobial resistance in food animals

HOW ANIMALS CAN PASS ON RESISTANT BACTERIA



AMR in food animals vs companion animals



AMR in humans attributable to food animals

- 1. AMR in zoonotic pathogens** (easy source attribution)
 - *Campylobacter*
 - *Salmonella*

- 2. AMR in commensal bacteria** that can cause opportunistic infections (difficult source attribution)
 - *Staphylococcus aureus* (clonal spread of AMR)
 - *E. coli* (horizontal transfer of AMR)

AMR in *E. coli* from food animals Denmark

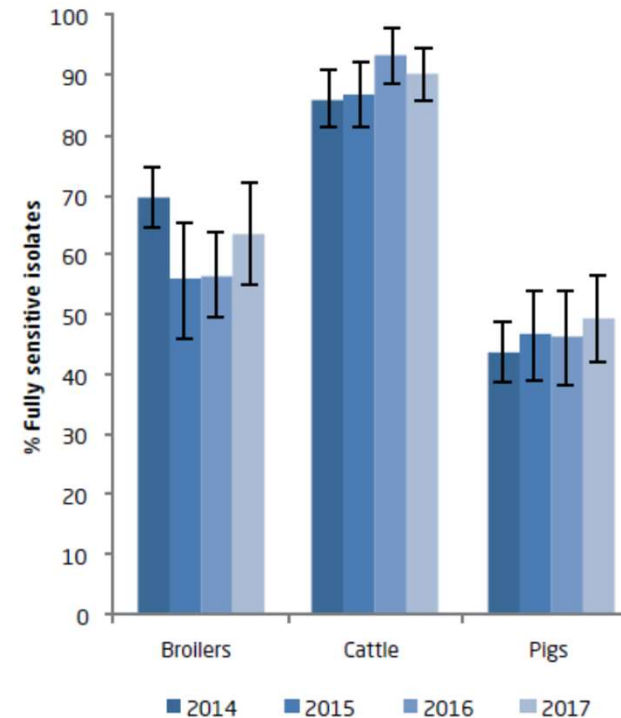
DANMAP 2017 (www.danmap.org)

Table 7.2 Resistance (%) among *Escherichia coli* from animals, Denmark DANMAP 2017

Antimicrobial agent	Broilers	Cattle	Pigs
	Danish %	Danish %	Danish %
Tetracycline	14	8	37
Tigecycline	0	0	0
Chloramphenicol	6	6	6
Ampicillin	17	6	36
Cefotaxime	0	<1	0
Ceftazidime	0	<1	0
Meropenem	0	0	0
Trimethoprim	17	2	30
Sulfonamide	17	7	35
Azithromycin	0	0	1
Gentamicin	3	<1	2
Ciprofloxacin	12	0	<1
Nalidixic acid	12	0	<1
Colistin	0	0	0
Fully sensitive (%)	63	90	49
Number of isolates	115	181	172

Note: An isolate is considered fully sensitive if susceptible to all antimicrobial agents included in the test panels

Figure 7.3 Proportion of fully susceptible *Escherichia coli* isolates from broilers, cattle and pigs, Denmark DANMAP 2017



Treatment of *Salmonella* and *Campylobacter* infections

- Usually no treatment (self-limiting infections)
- For severe infections (e.g. bacteremia)

- ***Salmonella***

- Ciprofloxacin (fluoroquinolone)
- Ceftriaxone (3rd gen cephalosporin)

- ***Campylobacter***

- Clarithromycin (macrolide)
- Ciprofloxacin (fluoroquinolone)



AMR in *Campylobacter jejuni* in Denmark DANMAP 2017 (www.danmap.org)

Table 6.2 Resistance (%) in *Campylobacter jejuni* isolates from animals, meat of Danish and imported origin and human cases^{a)}, Denmark

DANMAP 2017



Antimicrobial agent	Cattle	Broilers	Humans		Total %
	Danish %	Danish %	Domestically acquired %	Travel abroad %	
Tetracycline	7	16	22	68	32
Erythromycin	<1	0	1	6	2
Streptomycin	<1	0	0	-	-
Gentamicin	0	0	1	3	1
Ciprofloxacin	30	26	37	92	49
Nalidixic acid	30	26	37	92	49
Fully sensitive (%)	67	74	59	8	48
Number of isolates	236	43	252	79	397

a) An isolate is categorised as domestically acquired if the patient did not travel outside Denmark one week prior to the onset of disease

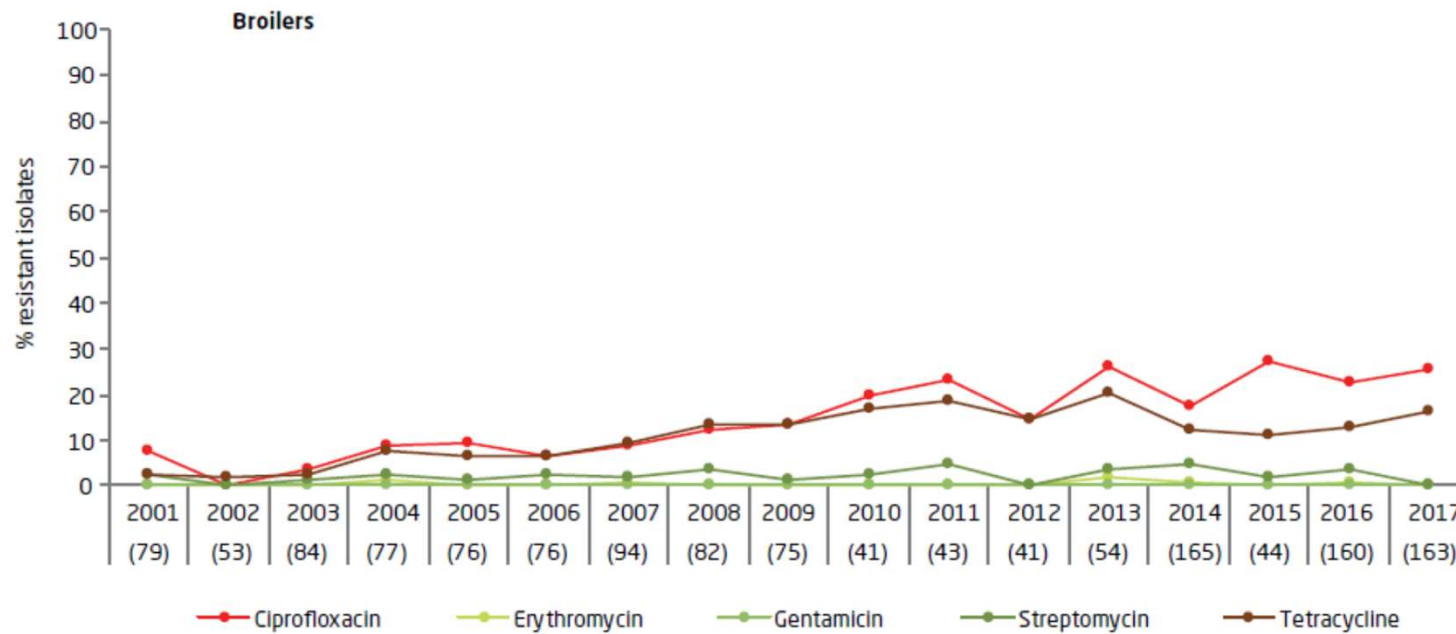


AMR in *C. jejuni* from broilers in Denmark

DANMAP 2017 (www.danmap.org)

Figure 6.4 Resistance (%) among *Campylobacter jejuni* from broilers, Denmark

DANMAP 2017



AMR in *Salmonella* Typhimurium in Denmark

DANMAP 2017 (www.danmap.org)

Table 6.1 Resistance (%) among *Salmonella* Typhimurium^(a) isolates from pigs, Danish pork and human cases^(b), Denmark DANMAP 2017

Antimicrobial agent	Pigs		Human cases		
	Danish %	Pork %	Domestically acquired %	Travel abroad reported %	Total %
Tetracycline	71	63	68	65	67
Tigecycline	0	0	<1	11	3
Chloramphenicol	5	19	17	11	13
Ampicillin	48	77	73	62	68
Cefotaxime	0	0	2	4	2
Ceftazidime	0	0	1	4	1
Meropenem	0	0	0	0	0
Trimethoprim	10	12	1	15	6
Sulfonamide	52	81	74	71	70
Azithromycin	0	2	0	5	1
Gentamicin	5	12	5	5	5
Ciprofloxacin	0	0	3	11	5
Nalidixic acid	0	0	<1	4	2
Colistin	0	0	<1	2	<1
Fully Sensitive (%)	19	14	22	24	22
Number of isolates	21	43	151	55	288

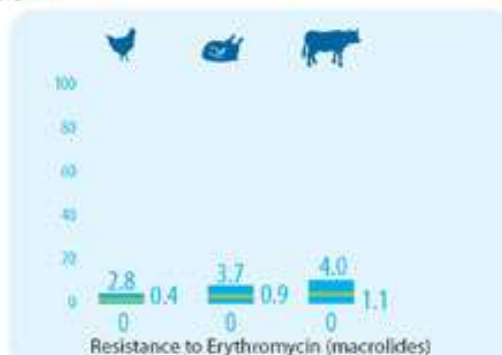


OVERVIEW OF RESISTANCE LEVELS IN EU

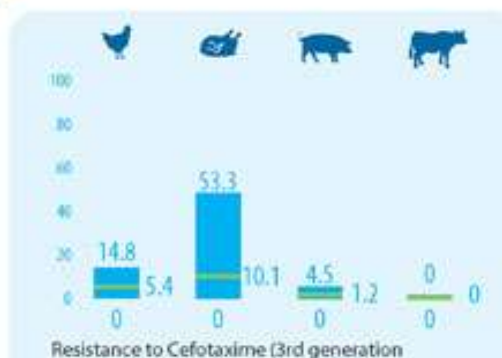
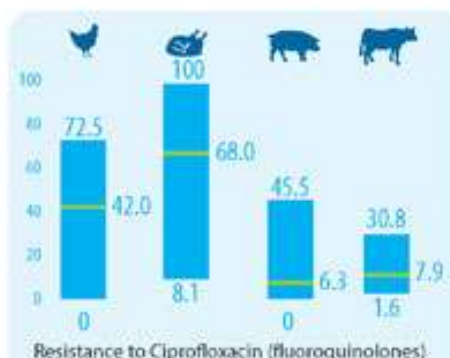
Based on "European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2013"

ANIMALS AND FOODS

Campylobacter jejuni



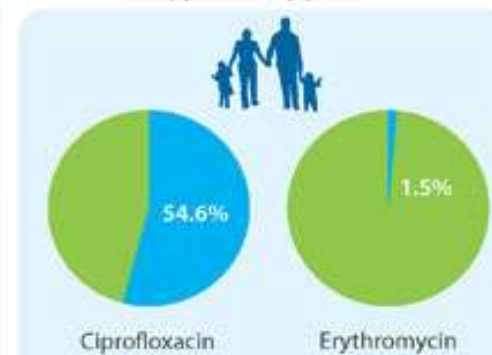
Salmonella



Variability in percentage of bacteria presenting microbiological resistance reported by Member States

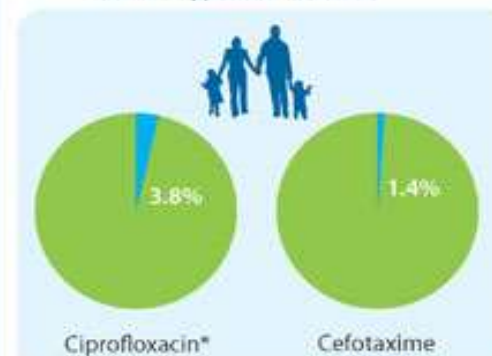
HUMANS

Campylobacter jejuni



Salmonella

(all non-typhoidal serovars)



■ resistant

* Interpretative criteria to establish clinical resistance were used in this case. If criteria to establish microbiological resistance were used, the results would be higher

Resistant bacteria impacting human health

ECDC (www.ecdc.europa.eu), DANMAP (www.sanmap.org)

AR Bacteria	No. deaths	No. Infections
MRSA	5,400	171,200
Vancomycin-resistant enterococci (VRE)	1,500	18,100
ESBL-producing <i>E. coli</i>	5,100	32,500
ESBL-producing <i>Klebsiella pneumoniae</i>	2,900	18,900
Carbapenem-resistant <i>P. aeruginosa</i>	10,200	141,900
TOTAL	25,100	386,100

Table 8.0.1 Distribution of species in invasive isolates (based on total number of isolates) and the percentage change from 2009 to 2017, Denmark
DANMAP 2017

Species	2009	2017	% change
<i>E. coli</i>	42.67%	46.60%	↑ 3.92%
<i>S. aureus</i>	16.89%	18.19%	↑ 1.30%
<i>S. pneumoniae</i>	12.03%	6.62%	↓ -5.41%
<i>K. pneumoniae</i>	9.93%	10.78%	↑ 0.85%
<i>E. faecium</i>	5.07%	7.23%	↑ 2.15%
<i>E. faecalis</i>	8.22%	6.18%	↓ -2.04%
<i>P. aeruginosa</i>	5.18%	4.41%	↓ -0.77%

“ESBL-bakterie” on Danish media

ESBL-bakterie er farligere end salmonella

Kolibakterien ESBL kan være livsfarlig, lyder det fra overlæge. En nationalovervågning sættes i gang i 2014.



ESBL findes i meget kylling, men har også mange andre smittetilgænder end kylling. © Colourbox

Dr.dk, 2014

A killer bug?

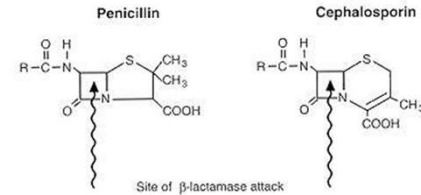


Dræberbakterie i svine- og oksekød

Danmarks førende forskere i bakterier vil have fjernet svine- og oksekød, der indeholder den potentielt dødelige ESBL-bakterie, fra danske butikker.

Jyllandsposten, 2008

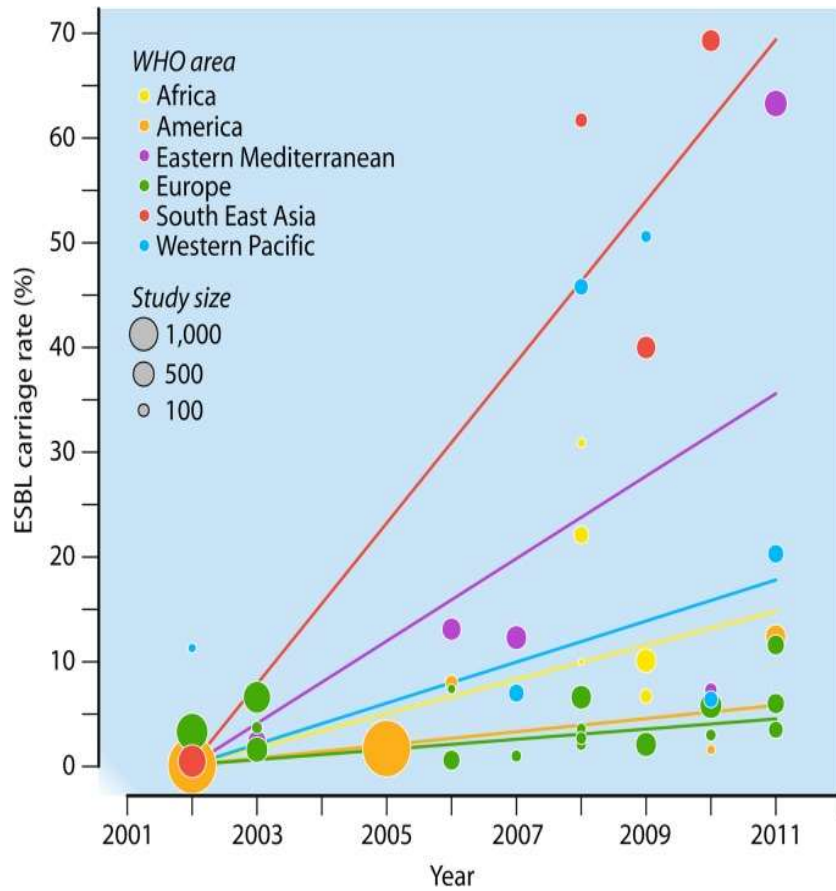
What is an ESBL?



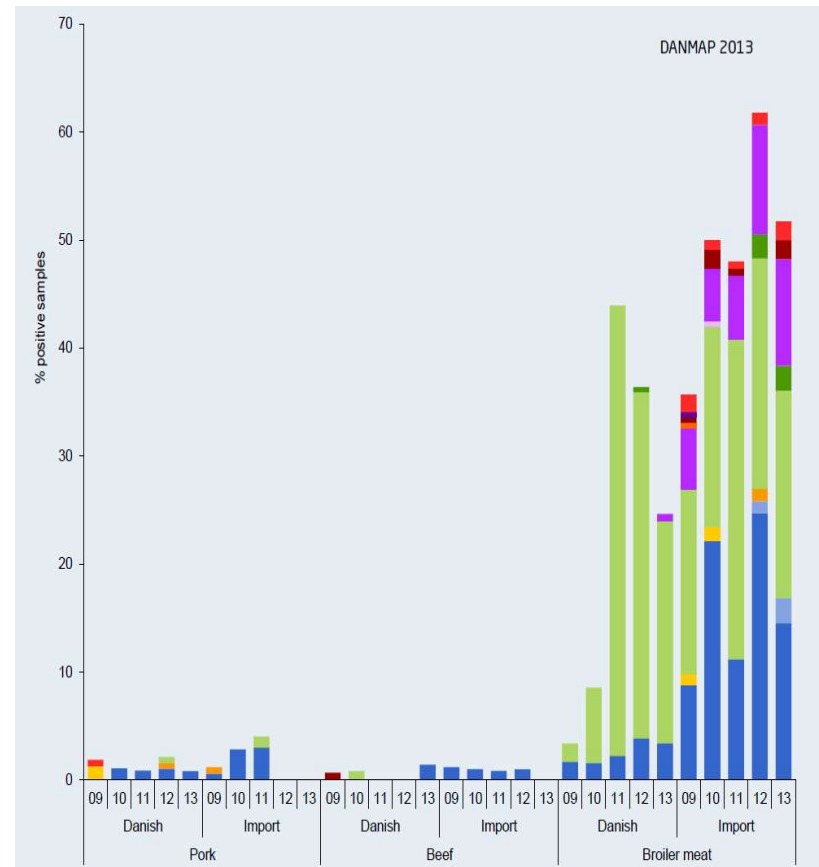
- It is an **enzyme** (extended-spectrum beta-lactamase) that **inactivates all β-lactams** (e.g. cephalosporins) except carbapenems
- It occurs in Gram-negative bacteria such as *E. coli*, rarely in *Salmonella*, where it spreads between different strains by **horizontal transfer of plasmids**
- Three main ESBL classes: **CTX-M**, TEM and SHV with CTX-M being the most common in both humans and animals
- Each ESBL class is composed of enzymes with slightly different sequence (e.g. **CTX-M has at least 128 types**)
- True ESBLs are inactivated by clavulanic acid, whereas **AmpC enzymes** that confer resistance to cephalosporins are not (e.g. **CMY-2**)

The ESBL epidemics

ESBL carriage rates in the community
Woerther et al. 2013



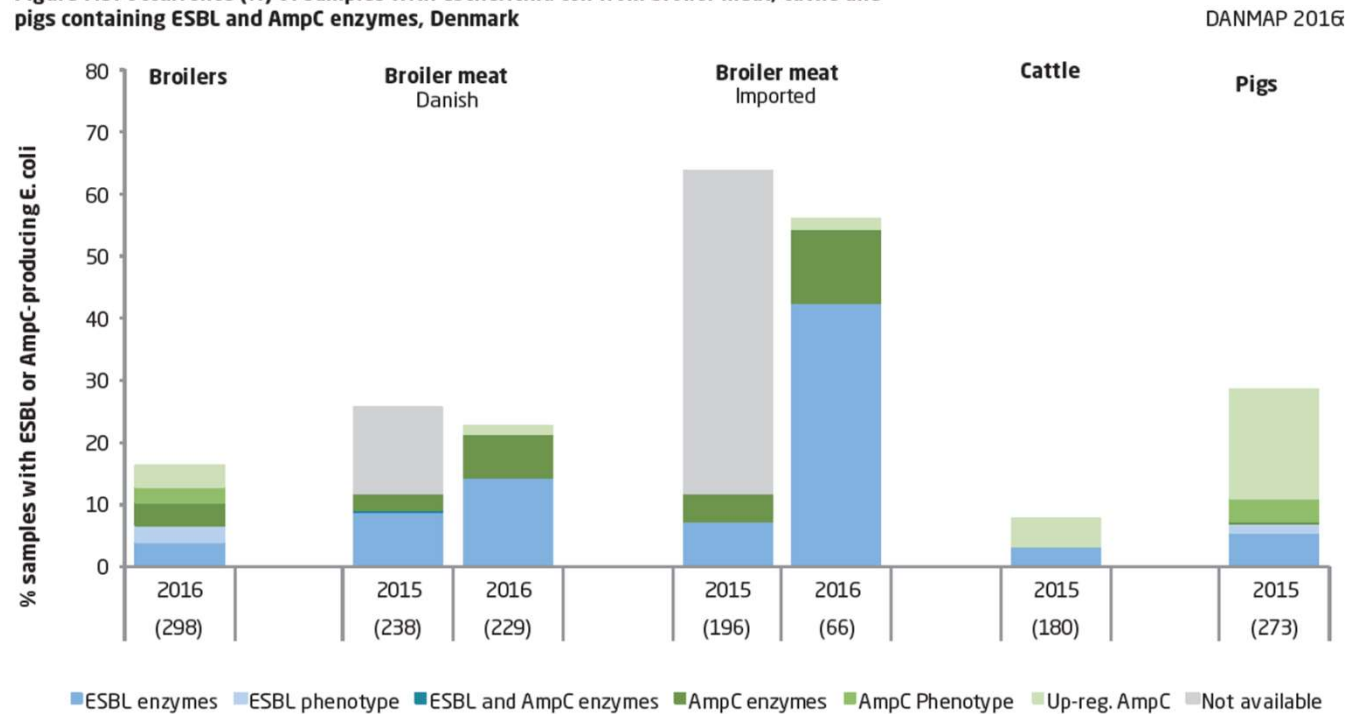
ESBL in *E. coli* from meat in Denmark
(www.danmap.org)



Frequency of ESBL/AmpC-producing *E. coli* in food animals in Denmark

DANMAP 2016 (www.danmap.org)

Figure 7.3. Occurrence (%) of samples with *Escherichia coli* from broiler meat, cattle and pigs containing ESBL and AmpC enzymes, Denmark



ESBL/CMY enzymes in *E. coli* in Denmark

DANMAP 2016 (www.danmap.org)

Broilers

Table 7.4. Distribution (%) of ESBL and AmpC enzymes detected in *E. coli* isolates^(b) from animals and meat of Danish and imported origin, Denmark DANMAP 2016

Enzyme	Broilers		Broiler meat
	Danish %	Danish %	Imported %
CMY-2	34	31	22
CTX-M-1	20	42	59
CTX-M-14b	0	0	3
SHV-12	3	8	8
TEM-52B	9	13	5
TEM-52C	3	0	0
Up-reg. AmpC	31	6	3

CMY-2 is infrequently detected and ST131 is the most common *E. coli* clone in human bloodstream infections. The opposite is seen for *E. coli* of animal origin, where the CMY is often detected, especially among broilers, and very few isolates belong to ST131 (DANMAP 2017).

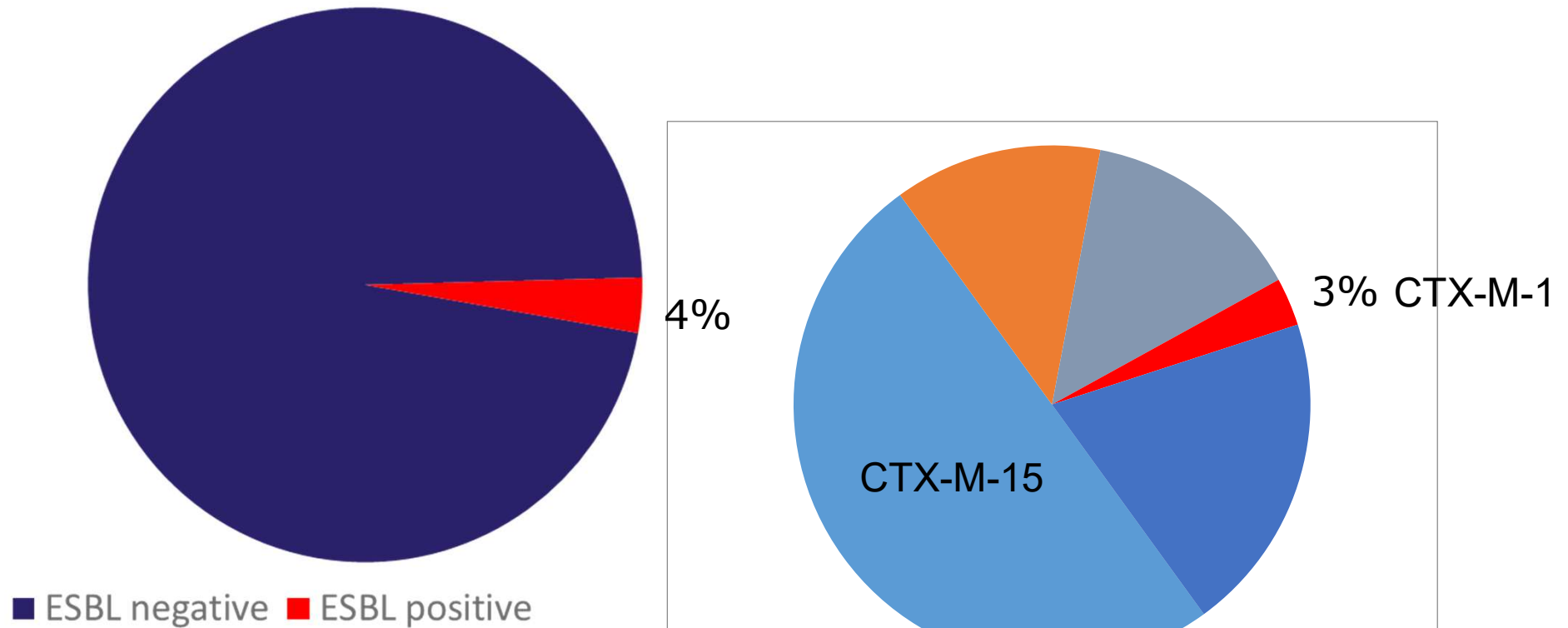
Human infections

Table 2. Most common ESBL/pAmpC enzymes and carbapenemases detected in *E. coli* from bloodstream infections, Denmark 2016 DANMAP 2016

Enzyme	DANMAP 2014		DANMAP 2015		DANMAP 2016	
	Number	%	Number	%	Number	%
CTX-M-15 ¹	121	49	139	51	157	50
CTX-M-27 ¹	25	10	33	12	44	14
CTX-M-14 ¹	38	16	33	12	40	13
CTX-M-101	12	5	15	5	14	4
CMY-2 ¹	10	4	6	2	10	3
CTX-M-14b	5	2	5	2	9	3
CTX-M-1	10	4	7	3	8	3
CTX-M-3 ¹	4	2	4	1	7	2
CTX-M-55 ¹	8	3	14	5	6	2
Other CMY variants ¹	4	2	10	4	3	1
Other ESBL enzymes	14	6	16	6	27	9
OXA-48-group ¹	3	1	3	1	1	0

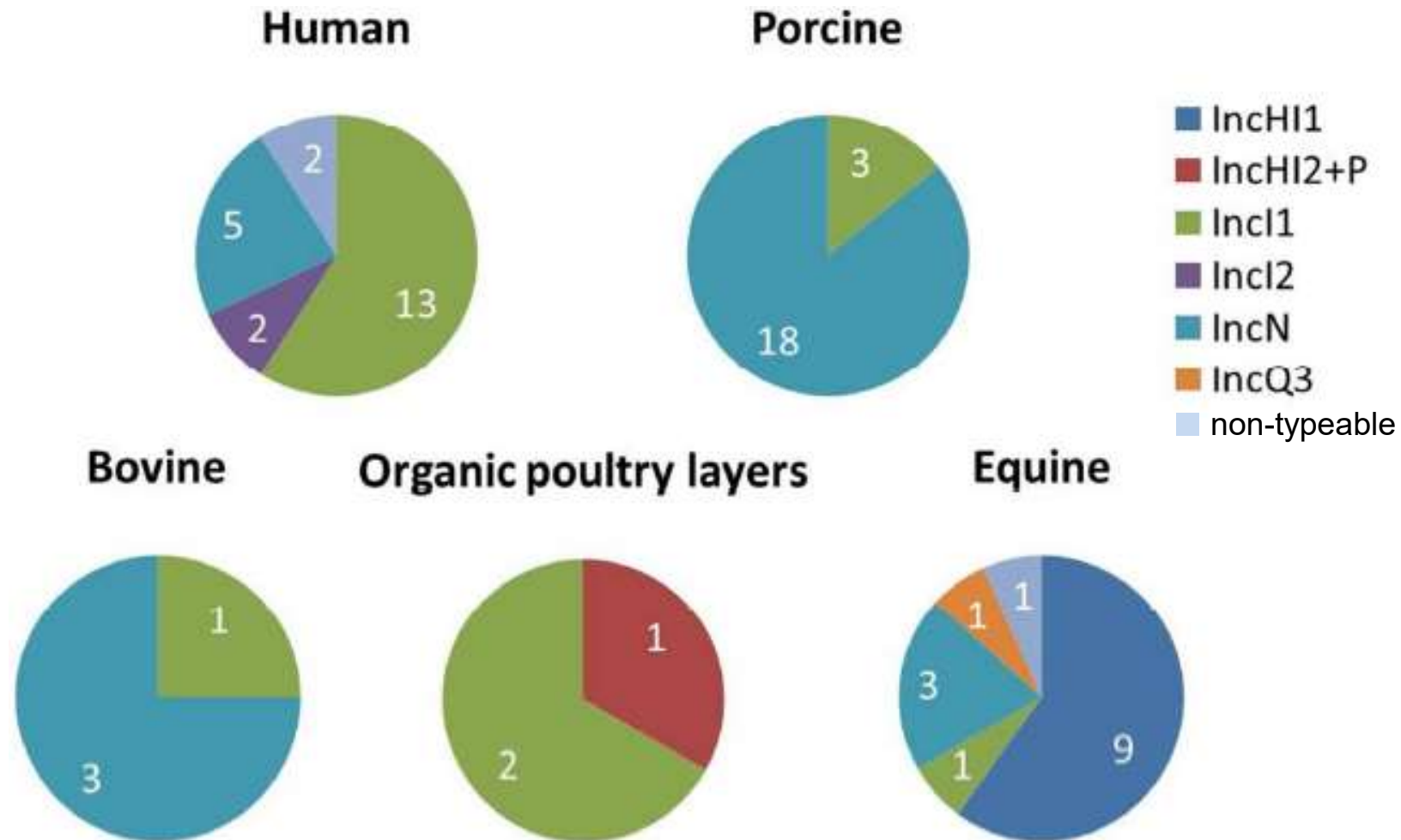
Frequency and type of ESBL-producing *E. coli* in community-acquired urinary tract infections in Denmark

Data from DANMAP(www.danmap.org)



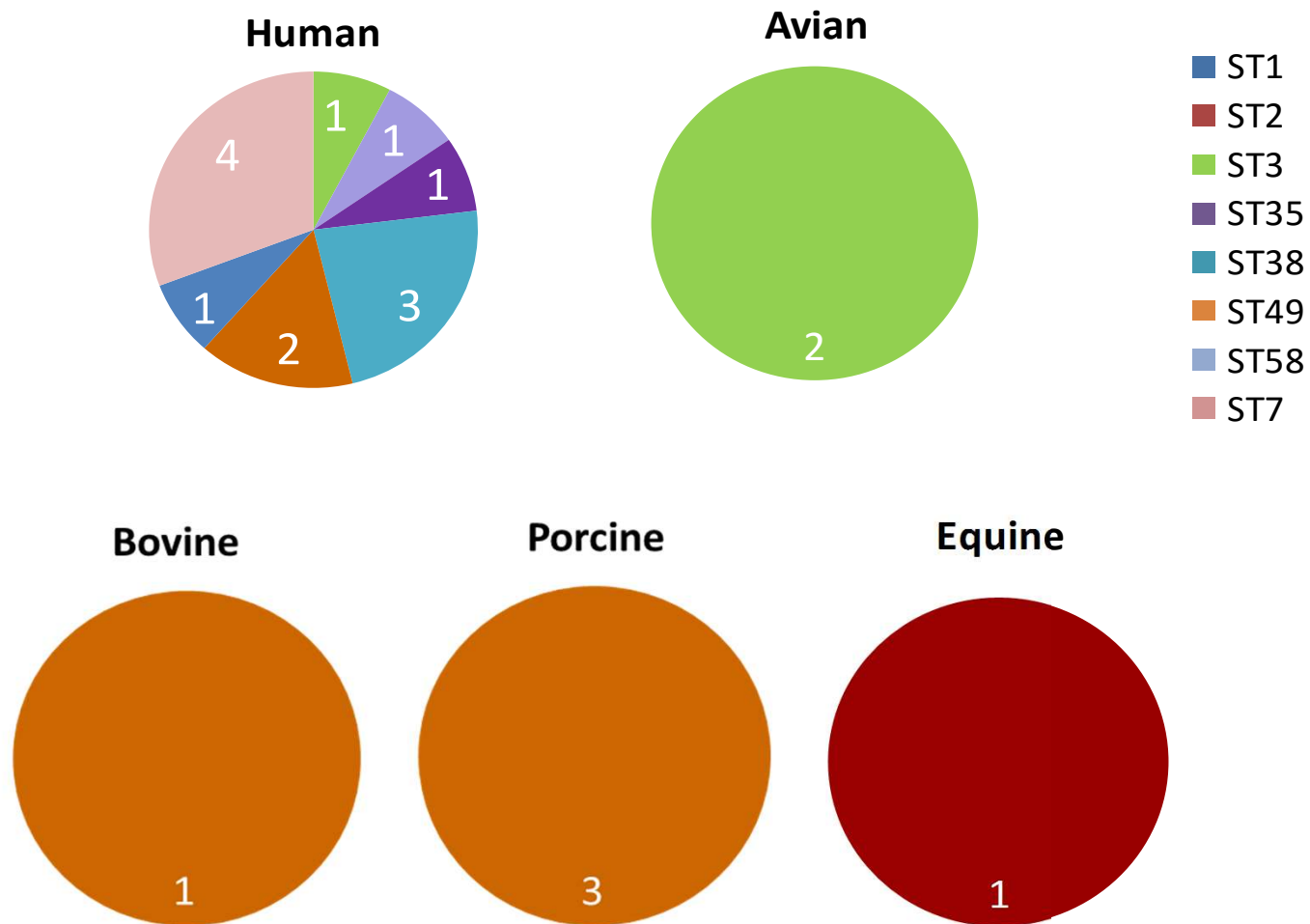
Limited similarity between CTX-M-1-encoding plasmids in *E. coli* from humans and animals in DK (2006-2010)

Jakobsen et al. JGAR 2015



Limited similarity between CTX-M-1-encoding plasmids in *E. coli* from humans and animals in DK (2006-2010)

Jakobsen et al. JGAR 2015



Take home messages

Antimicrobial use

- Denmark has a very low antimicrobial consumption, including CIAs
- Most antimicrobials are used in pigs, especially for post-weaning diarrhoea, where new alternatives to antimicrobials are needed in view of the planned phasing out of zinc in 2022
- **AMR**
 - AMR is not a big problem in zoonotic pathogens except for fluoroquinolone resistance in *Campylobacter jejuni*
 - The increasing occurrence of ESBLs in *E. coli* is the major concern for public health but source attribution is difficult
 - In Denmark ESBL-producing *E. coli* infections are rare compared to other countries and the vast majority is not related to animals