

Experiences and examples from the DANMAP

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DANMAP



DANMAP background: growth promoters and resistance

- In the 1990s, Danish scientists discovered that antimicrobial agents used as growth promoters in food animals lead to high occurrence of bacteria resistant to important antimicrobial agents used for human therapy in the animals
- Danish authorities banned the use of avoparcin and established a national surveillance programme (DANMAP)
- EU also banned growth promoters and member countries have now also established a similar surveillance program

The DANMAP program

–farm to fork to patients (One health)

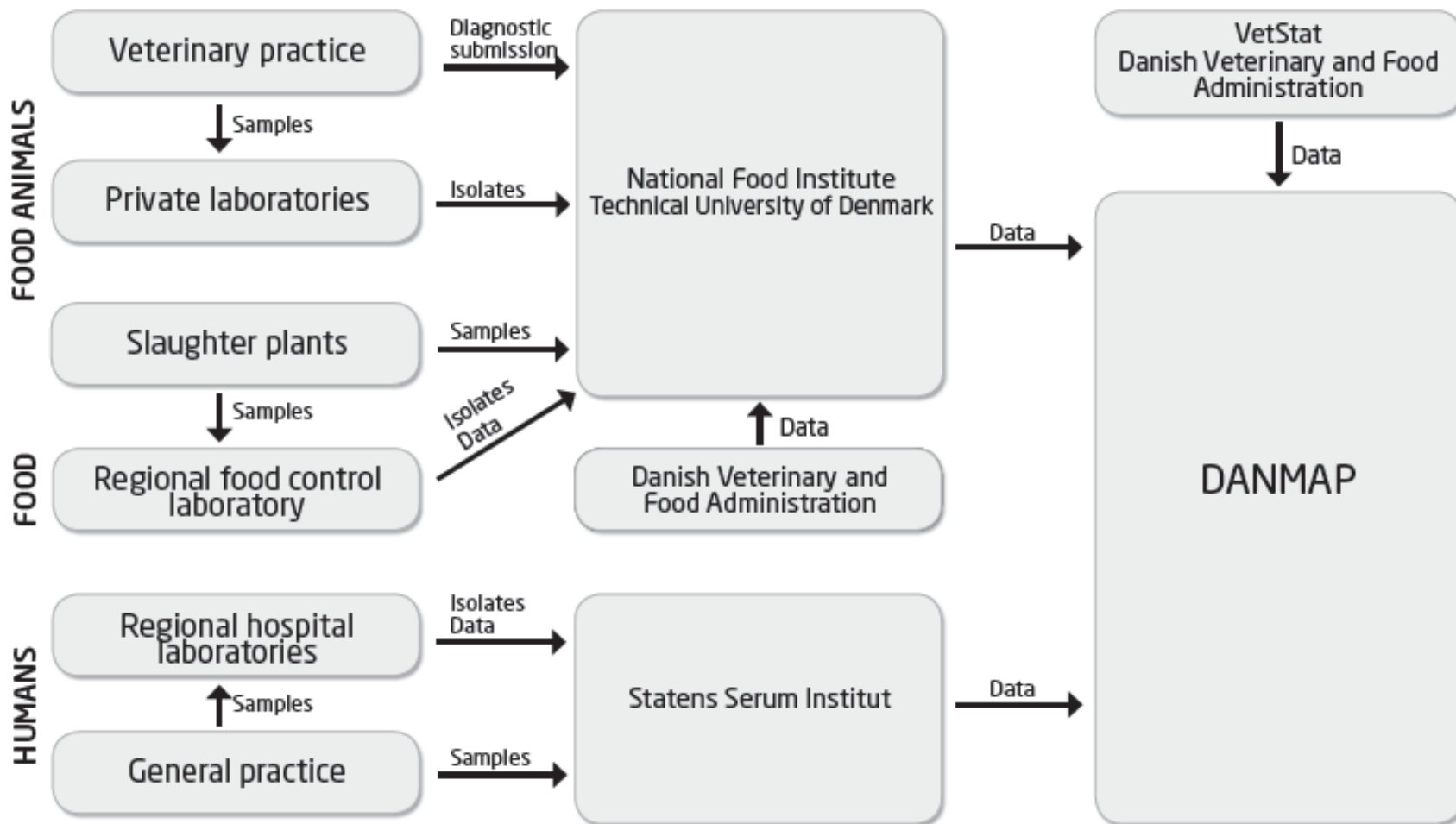
Initiated in 1995

Objectives

- Monitor consumption of antimicrobials for food animals (VetStat) and humans
 - VetStat was established in 2000 and collects data on prescribed medicine used in animals
- Monitor the occurrence of antimicrobial resistance among bacteria from food animals, meat and humans
- Study associations between antimicrobial consumption and antimicrobial resistance
- To identify routes of transmission and areas for further research

DANMAP

Figure 1.1. Organisation of DANMAP 2014



Running costs: < 1,0 mio. US\$/year

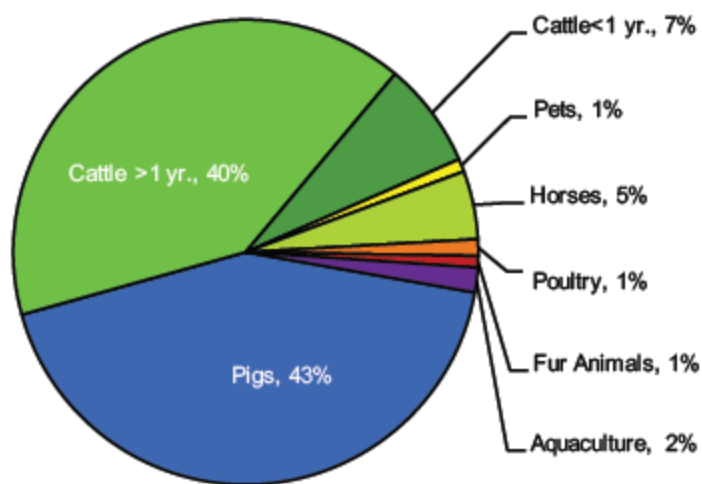
DANMAP: The bacteria

Three reservoirs: Food animals, food, and humans

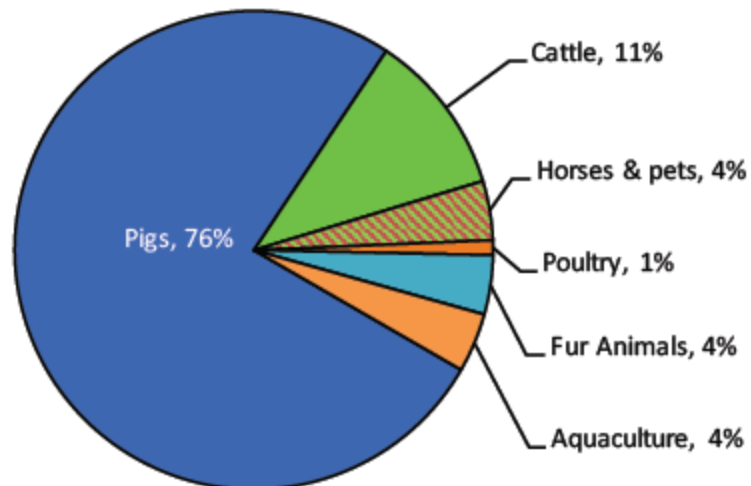
- Human and animal pathogens
 - Resistance reflects antimicrobial agents in these reservoirs
- Zoonotic bacteria
 - Develop resistance in the animal reservoir which may then compromise treatment effect when causing infection in humans
- Indicator bacteria (Enterococci and E. coli)
 - Ability to readily develop or transfer antimicrobial resistance in response to selective pressure in both reservoirs.

Veterinary consumption in 2014

- In 2014 the total consumption for animals was 114 tons and this value represented a 2% reduction from 2013

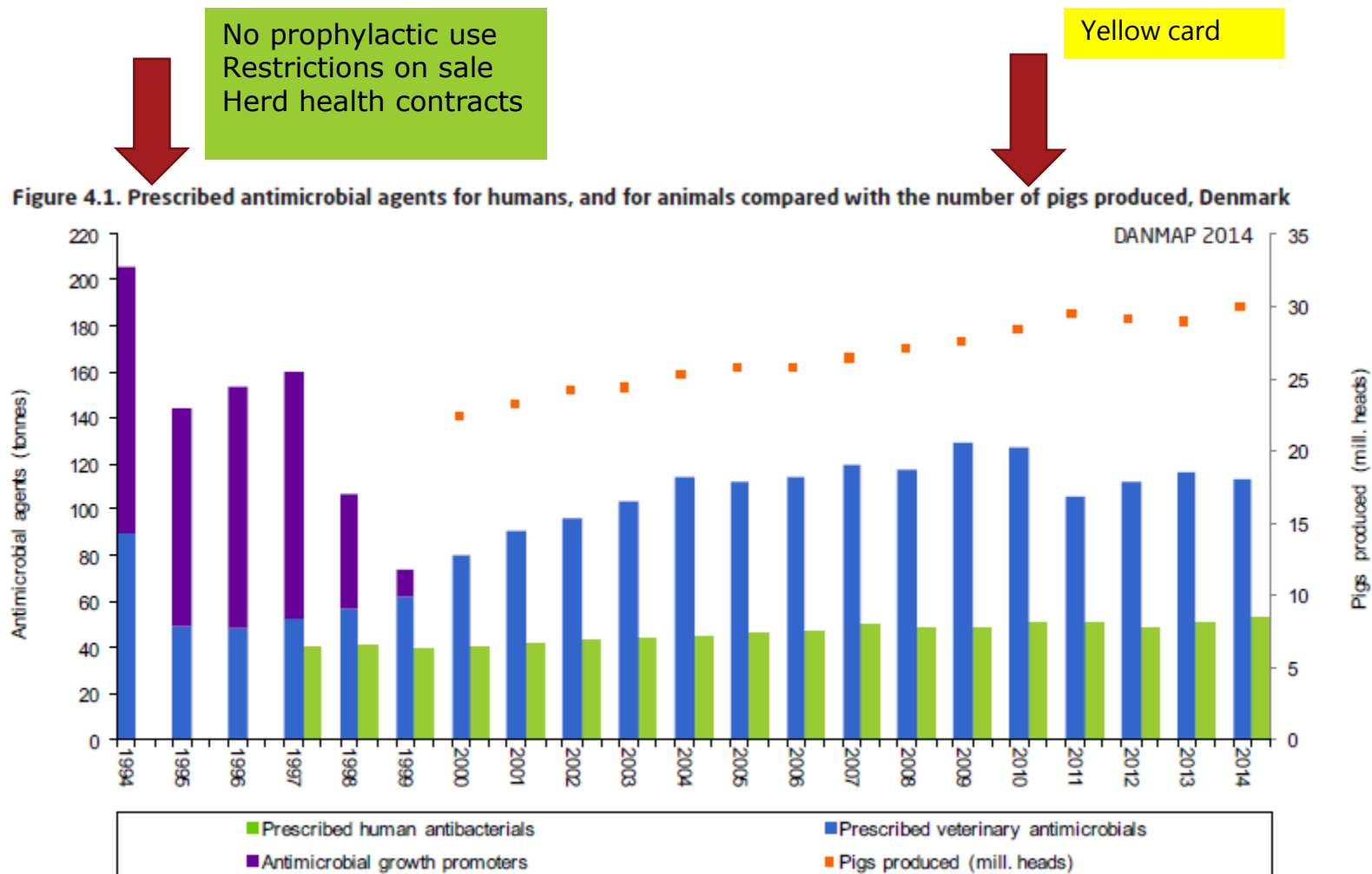


Live biomass



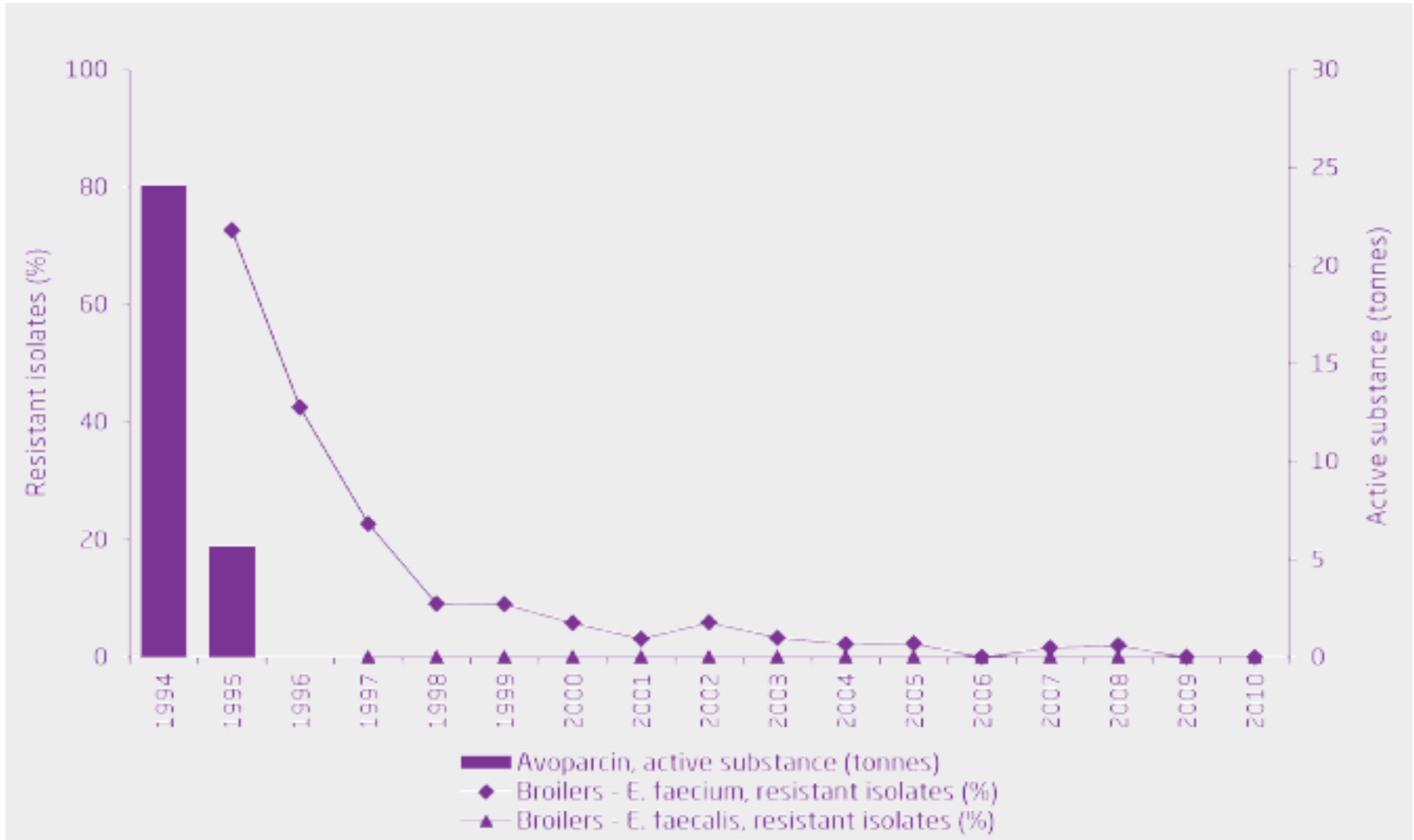
Kg active compound

Use of antibacterial agents in Denmark 1994-2014

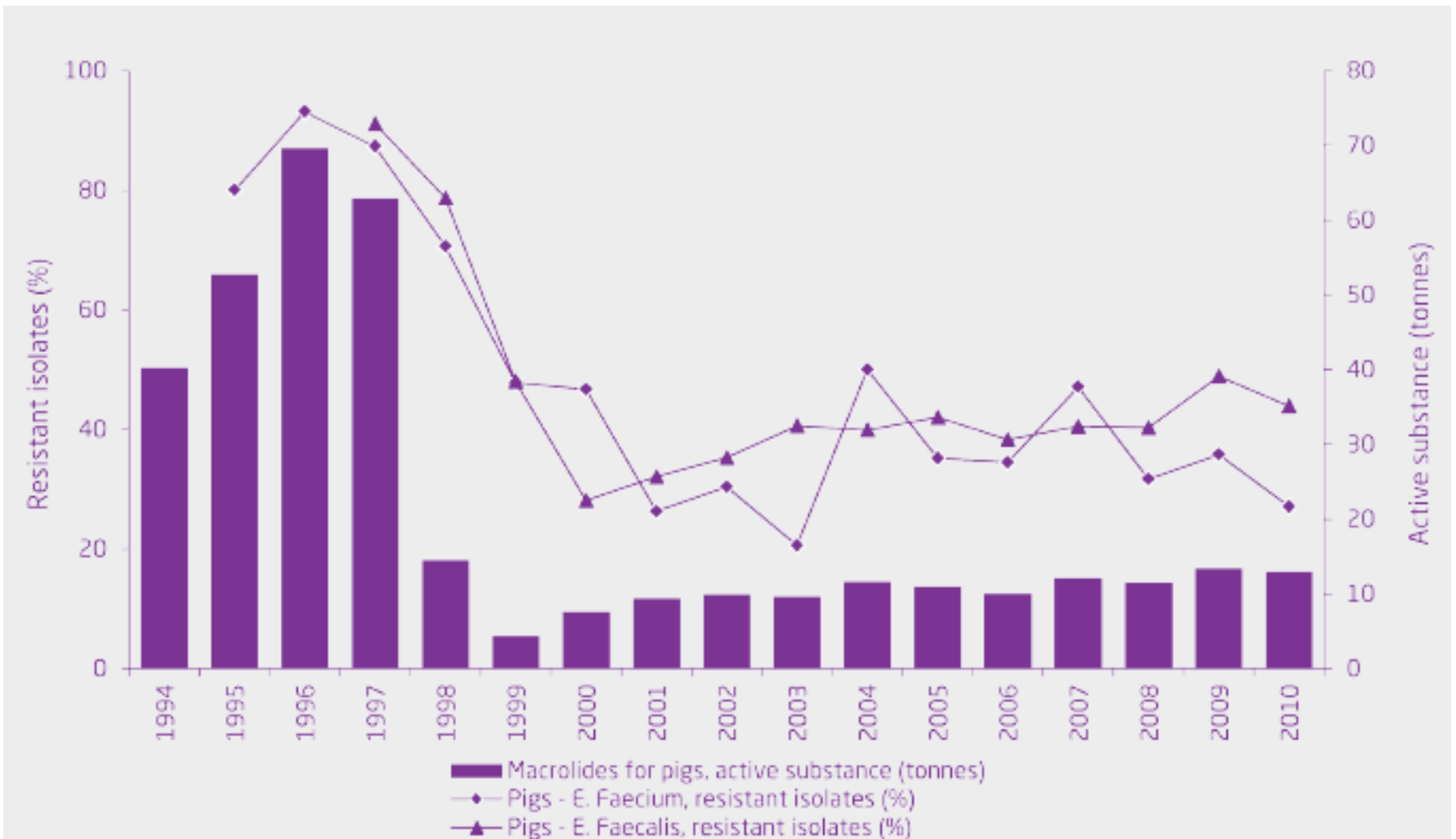


- The major species is swine (84% of meat production in 2013)
- The production of pigs has increased by 42% from 1996 to 2011.

Resistance to avoparcin decreases after the ban



Resistance to erythromycin follows the consumption

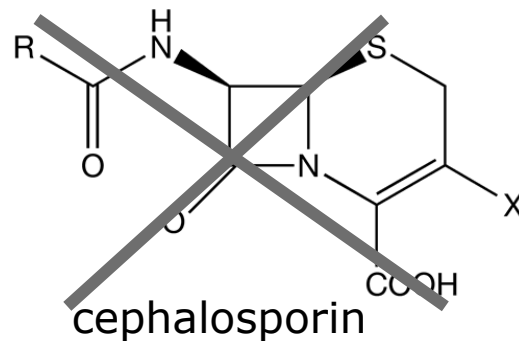


Effect of interventions in the pig production

**Yellow card
issued Dec 2010**



**Voluntary ban of cephalosporins
issued July 2010**



Yellow card

Political goal:

**10 % reduction in antimicrobial consumption by 2013
(ict. 2009)**

-basic aim is not to reduce the consumption of antimicrobials but to reduce the need for treatment with antimicrobials

	Post weaners (7 – 30 kg)	Pigs for slaughter (30 – 120 kg)	Breeding pigs (>120 kg)
National mean (ADD/100 animals per day)	14	4	2.6
Yellow Card Limit (ADD/100 animals per day)	28	8	5.2

Target 5 – 10 % of all swine farms in 2011

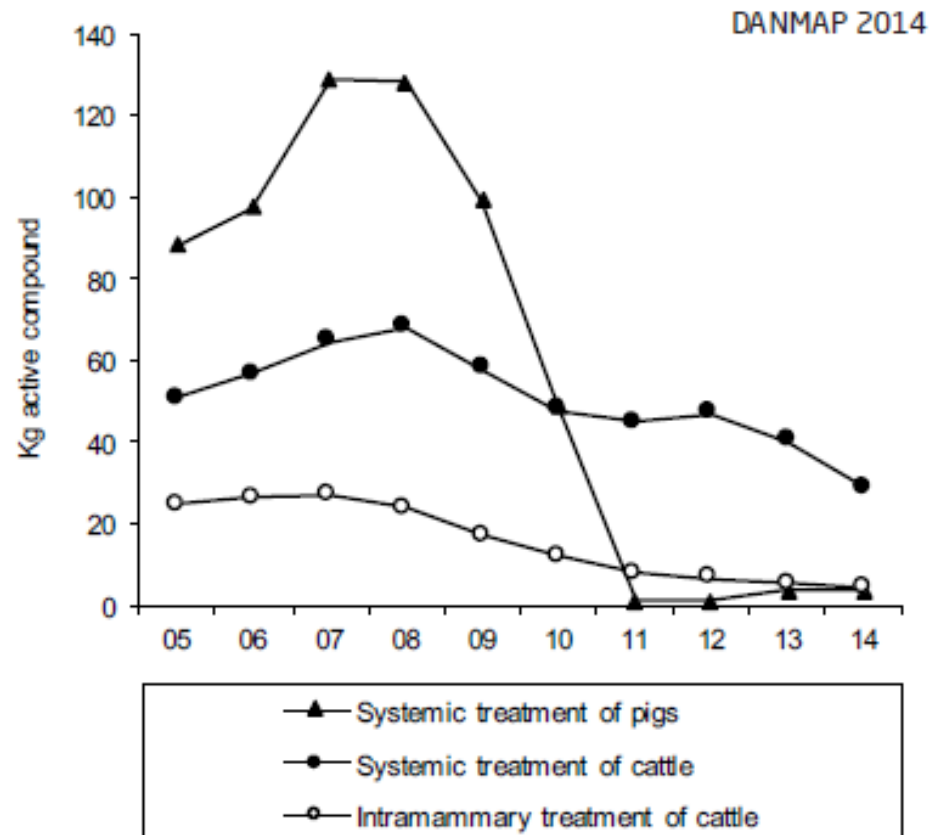
New Yellow card (since 30 june 2016)

- Dynamic process
 - Several adjustments done in 2013, 2014 and 2017. Values allowed along time- limits are now lower
- Similar principle but with weighted ADD on different drug classes:
 - Fluoroquinolones 10
 - Tetracyclines 1.2
 - Simple penicillins, sulphonamides, pleuromutilins 0.95
 - Remaining classes 1
- Political aim is to reduce use of critically important antimicrobials and of broad-spectrum drugs, ex tetracyclines

Use of critically important drugs in production animals

- 3rd and 4rd generation cephalosporins:
 - Pigs: reduced to nearly zero (4 kg).
 - Cattle: reduced since 2008 but used systemically and intramammary
 - Poultry: No use
- Fluoroquinolones (19 kg):
 - 40% (9 kg) pets
 - Pigs (4 kg) (clinical trial ended)
 - Horses (6 kg)

Figure 4.5. Consumption of 3rd and 4th generation cephalosporins in pigs and cattle, Denmark



Consumption in pets

- The use of antimicrobials for pets is increasing since 2005, e.g. increased use of amoxicillin with clavulanic acid
- Increase in fluoroquinolones usage
- Critically important drugs make up 5-10% which is considered important because of health risk for owners

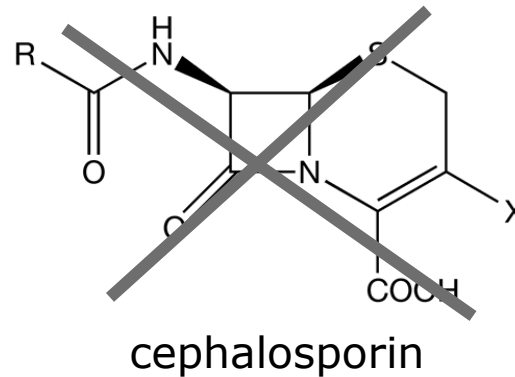


Summary on veterinary use of antimicrobials

- Increasing demands for use of antimicrobials in pigs in swine production along time...
- Low use of critically important antimicrobials such as cephalosporins and fluoroquinolones for production animals
- Increase in total use for pets but reduction in critically important drugs, however some risk
- Some 3rd and 4rd generation cephalosporin usage in cattle

ESBL/ESC (Extended spectrum cephalosporinase)

- In DANMAP 2009 “ESBL” describes the clinically important acquired beta-lactamases with activity against extended-spectrum cephalosporins; including the classical class A ESBLs (**CTX-M, SHV, TEM**), the plasmid-mediated **AmpC** and OXA-ESBLs. [Giske *et al. JAC 63:1-4*].

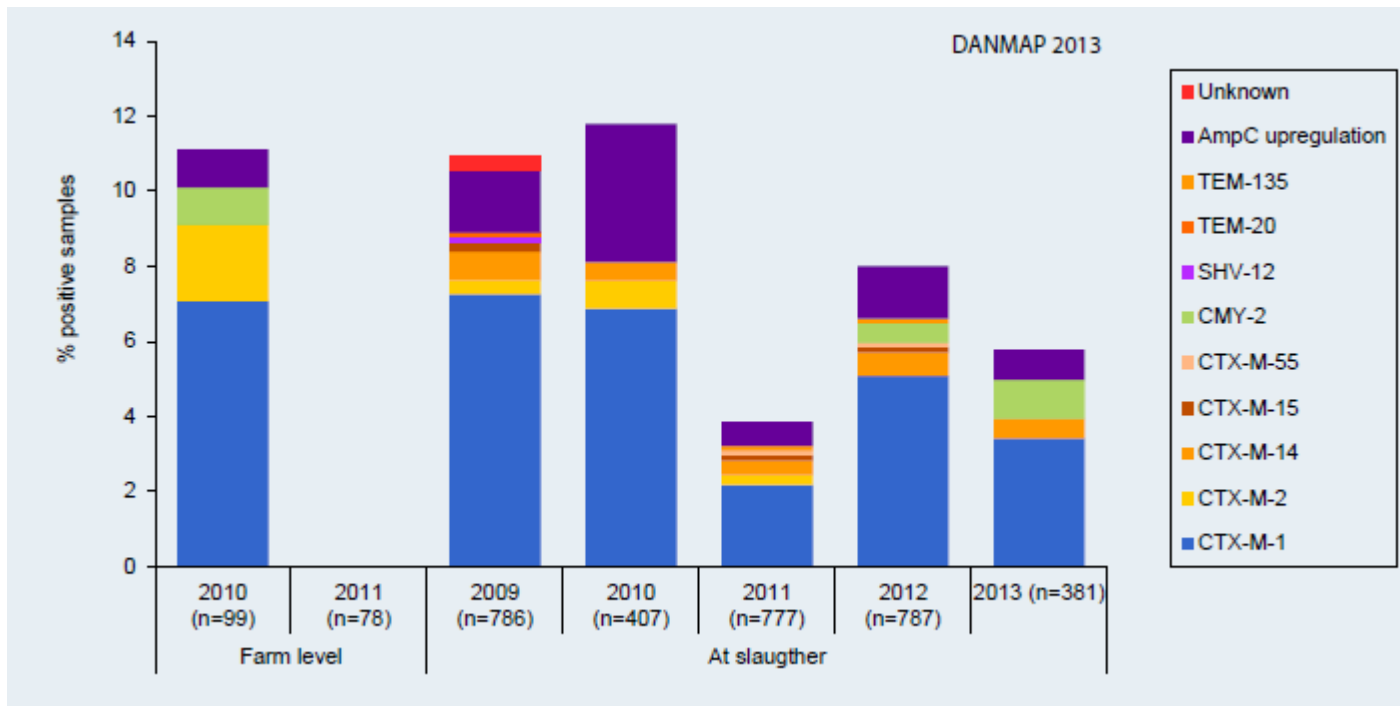


Main question:

Has the removal of cephalosporins reduced ESBL in pigs?

ESBL-producing *E. coli* in animals—selective isolation procedures

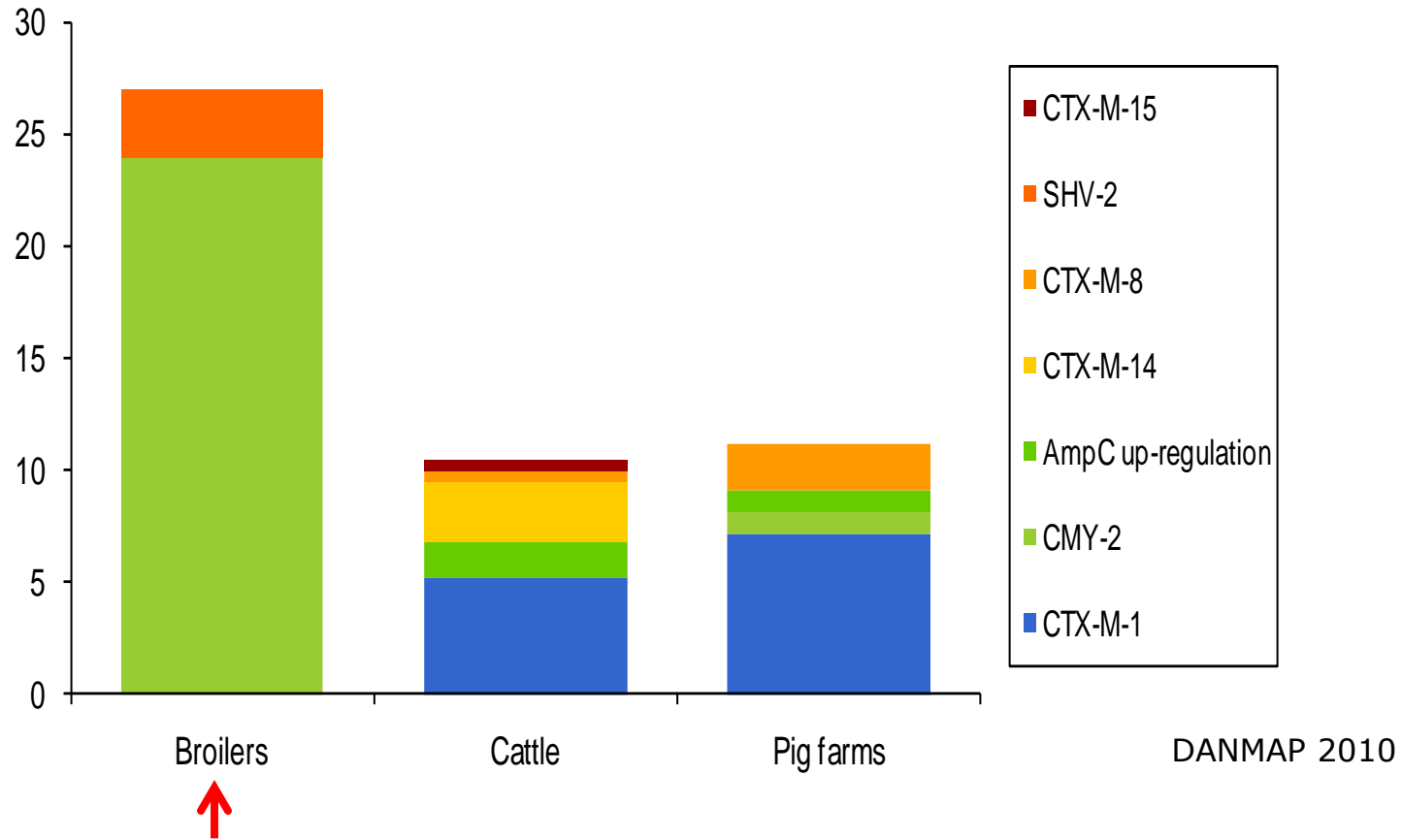
Voluntary cephalosporin ban enforced



When resistance does not reflect the national usage pattern

- Example 1: Imported resistance
- Example 2: Dominating clones and shift in control programmes

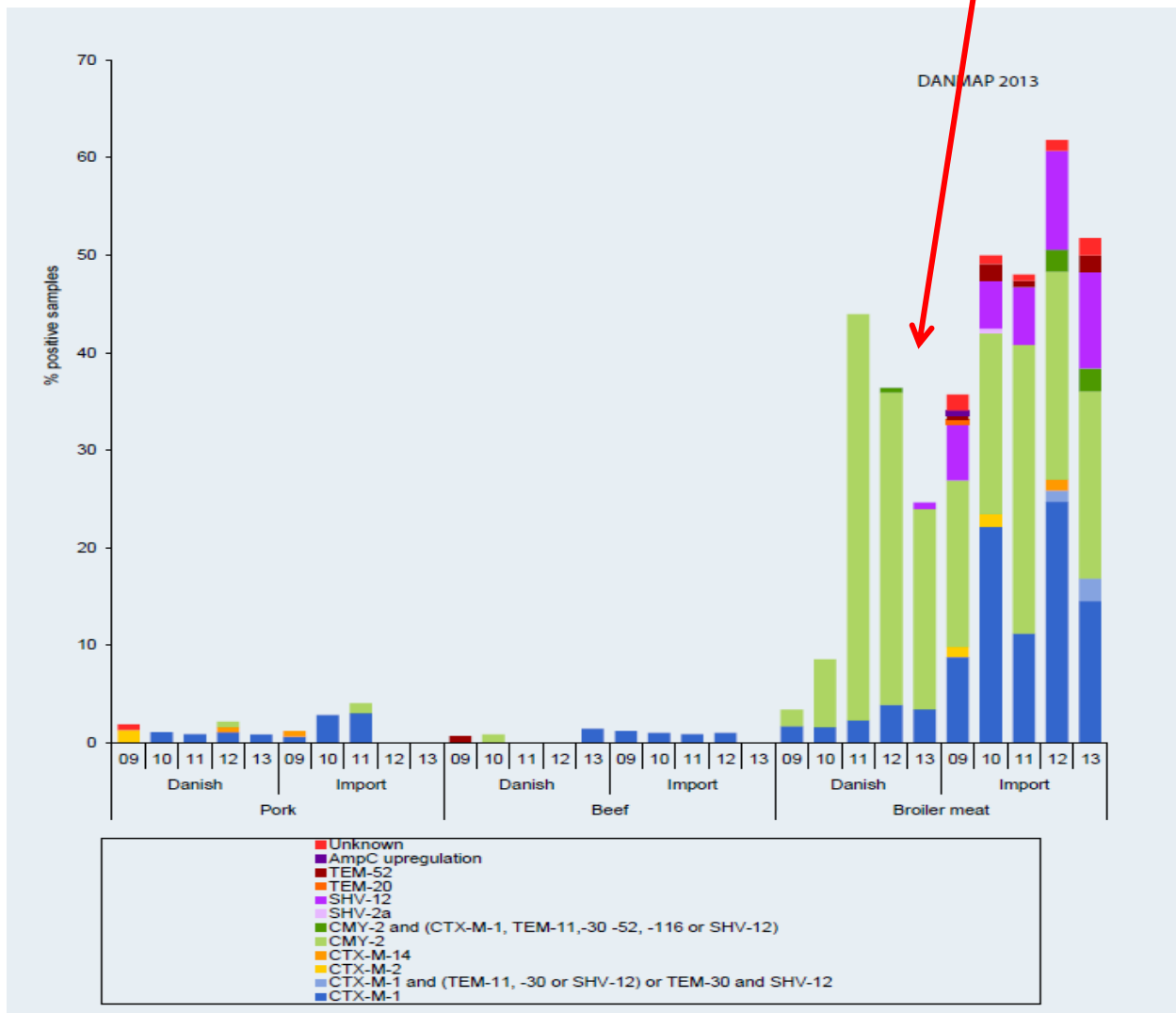
ESBL *E. coli* in broilers, pigs and cattle 2010



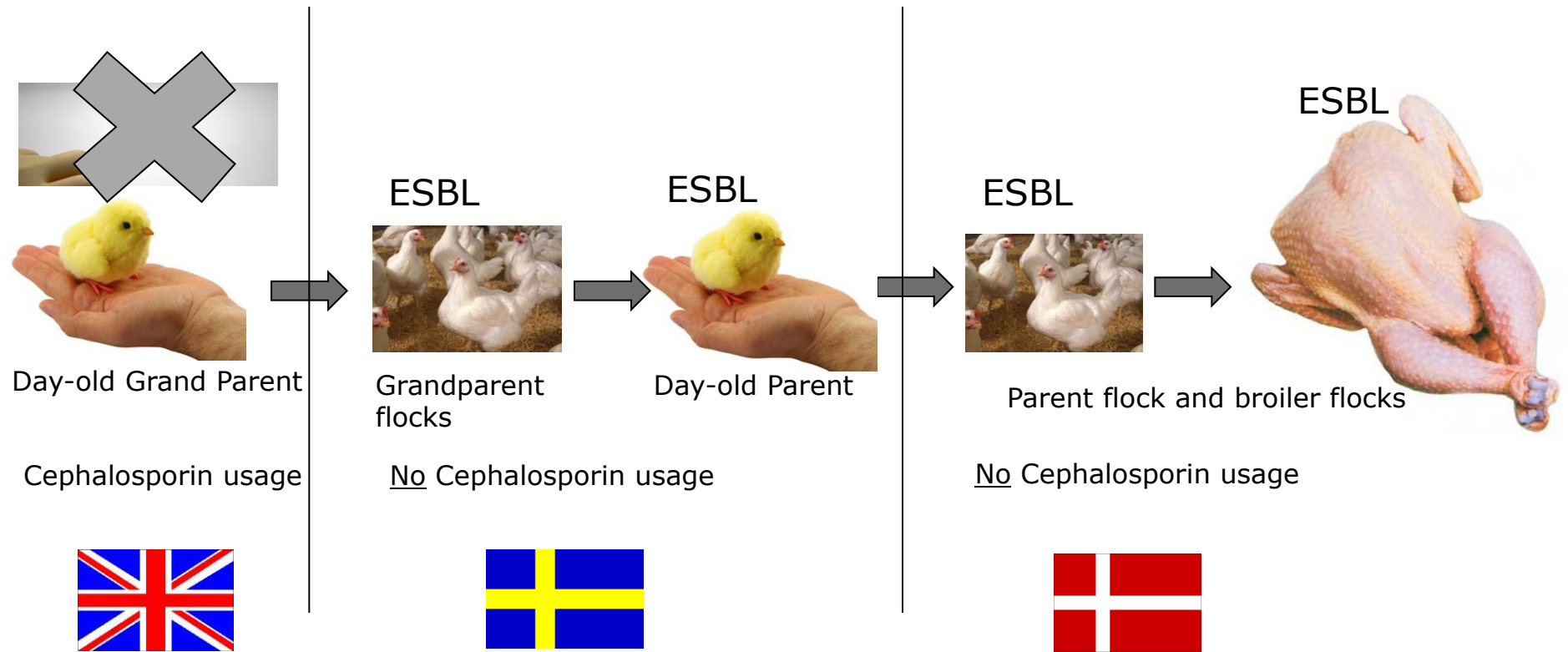
Cephalosporins have not been used for broilers in DK for at least 10 years

ESBL-producing *E. coli* in meat – selective enrichment results

Significant decrease



The Danish broiler production pyramid

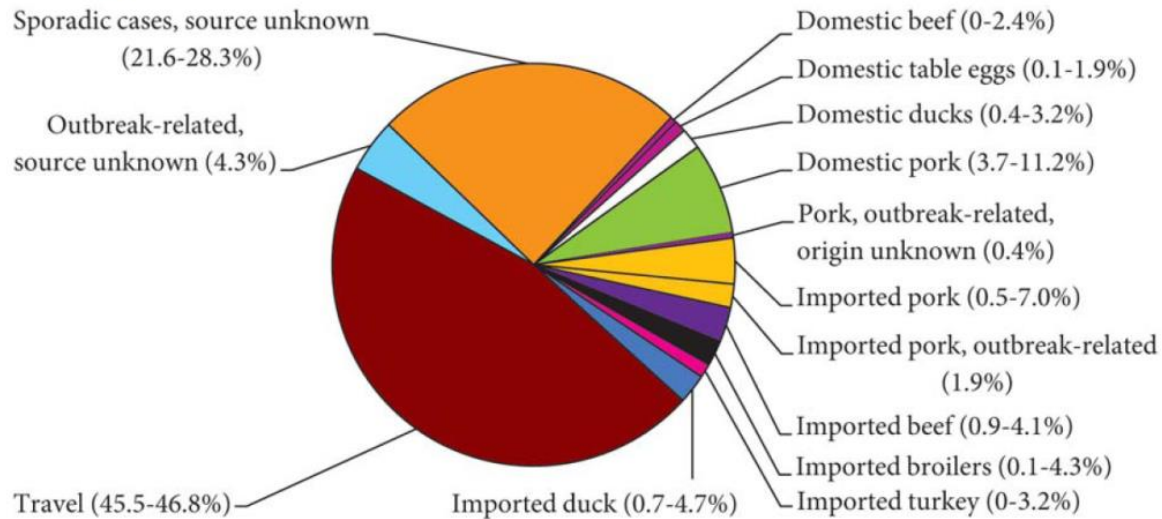


Usage in one country can affect resistance in another country

Zoonotic link and sources

Source attribution for Salmonella:

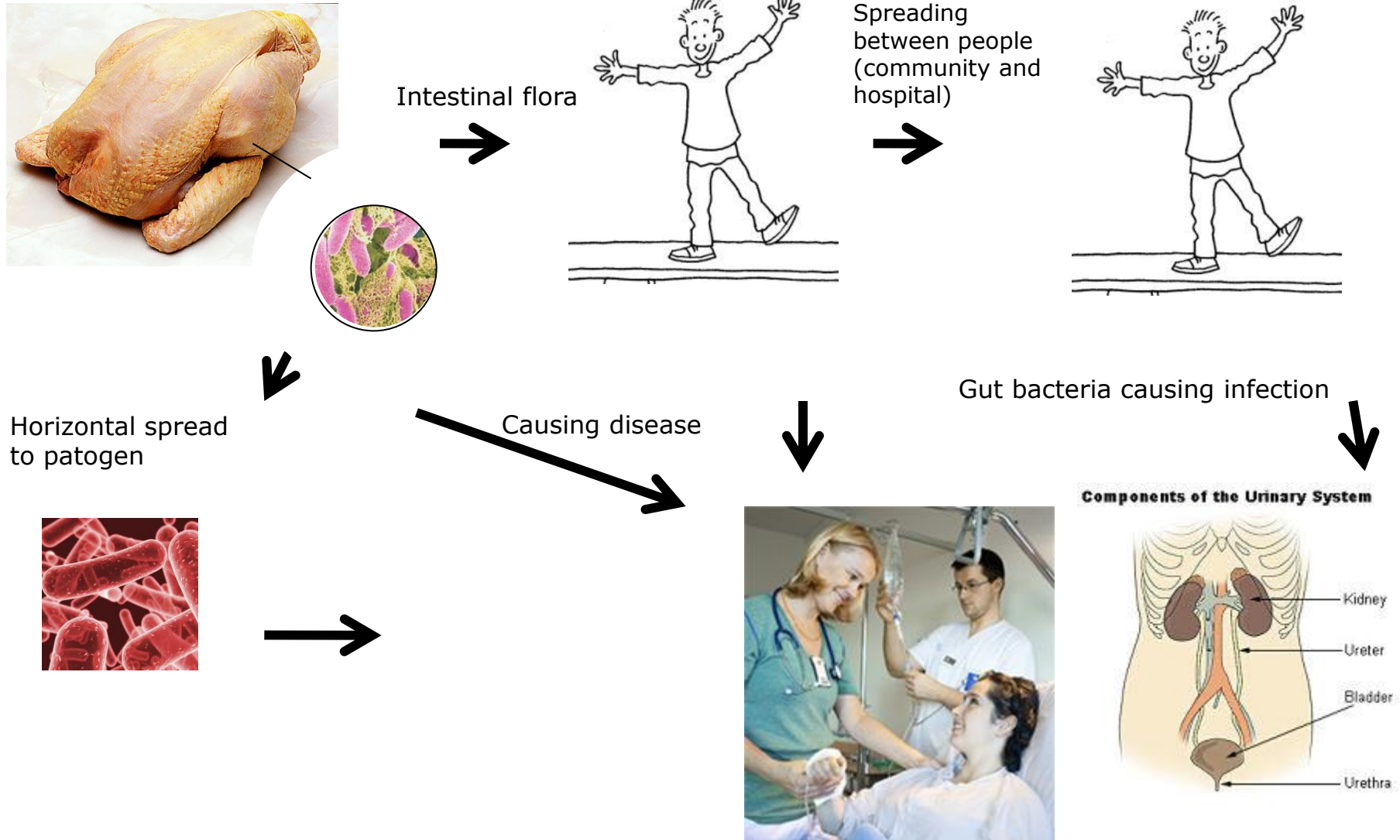
Figure 1.2. Estimated sources of 1,166 cases of human salmonellosis in Denmark, 2011
(See also Appendix A, Table A1)



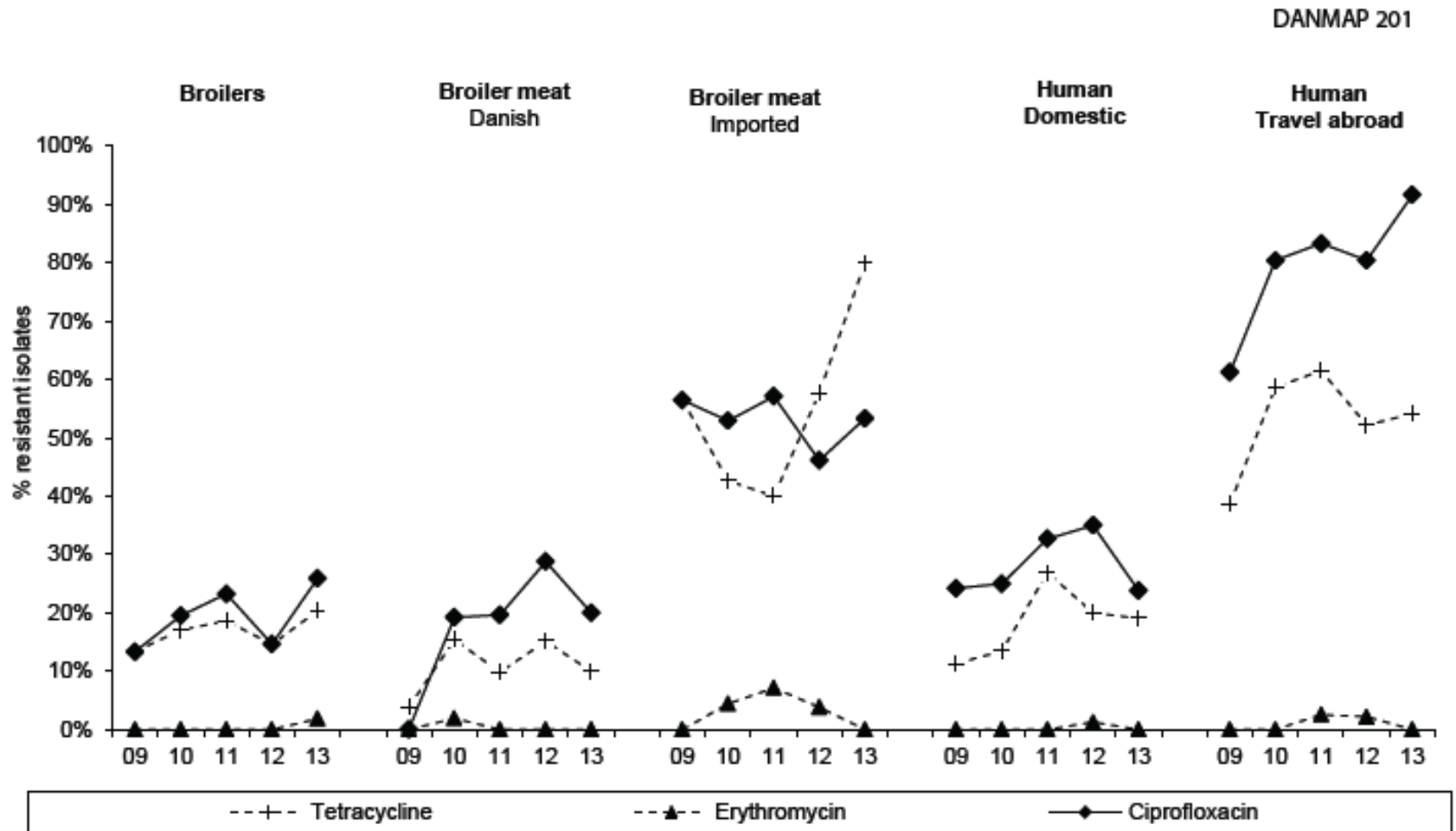
How large a proportion of ESBL in humans originates from animals?

- Case reports
- Epidemiology
- Comparison of isolates, genes, mobile elements from animals, meat/food and humans

Can we quantify horizontal transferable resistance like ESBL *E. coli* from broilers?



Imported resistance



Conclusions

- Measurements of correlation between consumption and resistance requires knowledge **about epidemiology and microbiology**.
 - Introduction via imported live animals
 - Introduction via imported meat or human movement
 - Introduction and spread of ESBL clones and selective factors
- The voluntary stop for use of **cephalosporins** has effectively reduced the consumption of cephalosporins and the occurrence of ESBL has dropped significantly.
- The usage of cephalosporins in other countries has led to a high occurrence of ESBL in broiler meat-so consumption in one country influence the ESBL situation in other countries.
- ESBL is dynamic and we should not wait for quantitative data on risk for humans. Unnecessary and systematic use of cephalosporins which has taken place (and takes place) have to stop.

Carbapenemase-producers in animals and their environment

Acinetobacter
OXA-23



Poirel et al. EID 2012.
France 2011



Acinetobacter
OXA-23



Kempf et al. PloS one 2012.
Senegal 2012



Acinetobacter
NDM-1



Wang et al. PloS one 2012.
Zhang et al. JAC 2013.
China 2012, 2013

J Antimicrob Chemother
doi:10.1093/jac/dks108

***Escherichia coli* producing VIM-1 carbapenemase isolated on a pig farm**

Jennie Fischer¹, Irene Rodriguez², Silvia Schmagor¹, Anika Friese¹, Uwe Roesler¹, Reiner Helmuth¹ and Beatriz Guerra^{1*}

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J Antimicrob Chemother
doi:10.1093/jac/dks393

***Salmonella enterica* subsp. *enterica* producing VIM-1 carbapenemase isolated from livestock farms**

Jennie Fischer¹, Irene Rodriguez², Silvia Schmagor¹, Anika Friese¹, Uwe Roesler¹, Reiner Helmuth¹ and Beatriz Guerra^{1*}

¹Department for Biological Safety, Federal Institute for Risk Assessment (BfR), Max-Dohm-Strasse 8-10, D-10589 Berlin, Germany; ²Institute for Animal Hygiene and Environmental Health, Free University Berlin (FU), Robert-von-Osterlog-Strasse 7-13, D-14163 Berlin, Germany

J Antimicrob Chemother
doi:10.1093/jac/dks1260

NDM-1 carbapenemase-producing *Salmonella enterica* subsp. *enterica* serovar Corvallis isolated from a wild bird in Germany

Jennie Fischer, Silvia Schmagor, Silke John, Reiner Helmuth and Beatriz Guerra*

Acinetobacter OXA-23



Smet et al. JAC 2012.
Belgium 2012

E. coli NDM-1



Shaheen. AAC 2013.
USA 2013

E. coli and *Klebsiella* OXA-48



Stolle et al. JAC 2013.
Germany 2013

DANMAP: collaboration, trust, quality data, control

- Each animal production farm has a unique ID number
- Antimicrobials can only be prescribed by veterinarians to a farmer who then obtain the drugs at the pharmacy
- Each veterinarian has an ID number and DOES NOT make money on drugs!
- Veterinarians makes money on advisory services (herd health contracts)
- Pig farmers are well organized (cooperatives)
- Mutual trust and respect
- Quality assured and comparable AMR testing (automated MIC testing)
- Skilled and experienced government control personnel

Separation of risk assessment and risk management

Integrated collaborate program

- Microbiologists, physicians, veterinarians and epidemiologists – assess risks
- Danish Veterinary and Food Administration, Danish National Board of Health conduct risk management

Conclusions

- **Resistance spreads globally –therefore it is everybody's concern**
 - **BUT local/national control efforts are EFFECTIVE**
- **Actions that works**
 - No profit from sales
 - Restrictions on use
 - Control based on consumption
 - Restrictions should be done together with improvement of management (hygiene, disease prevention (e.g. vaccines), welfare)
- **Focus on**
 - Targeting the worst antimicrobials
 - Prevent diseases
 - Improve hygiene (management in herds, slaughter line, kitchen, hospitals)
 - Improvement of treatment strategies (to prevent resistance)
 - **Always surveillance in combination with interventions!!**

What would be most effective in Vietnam?

- Questions?

Thank you!

- **Acknowledgements**

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