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Antimicrobial stewardship in veterinary medicine

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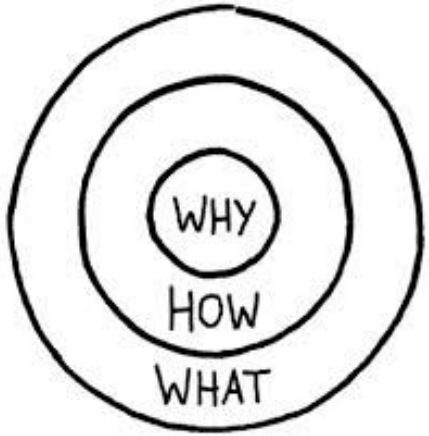
VINORDIC course on One Health, Rungstedgaard, 31st January 2019

Lecture outline

- What is an antimicrobial stewardship (AS)? (the WHAT)
- Why is AS needed in veterinary medicine (the WHY)?
- How can AS be implemented in veterinary medicine (the HOW)



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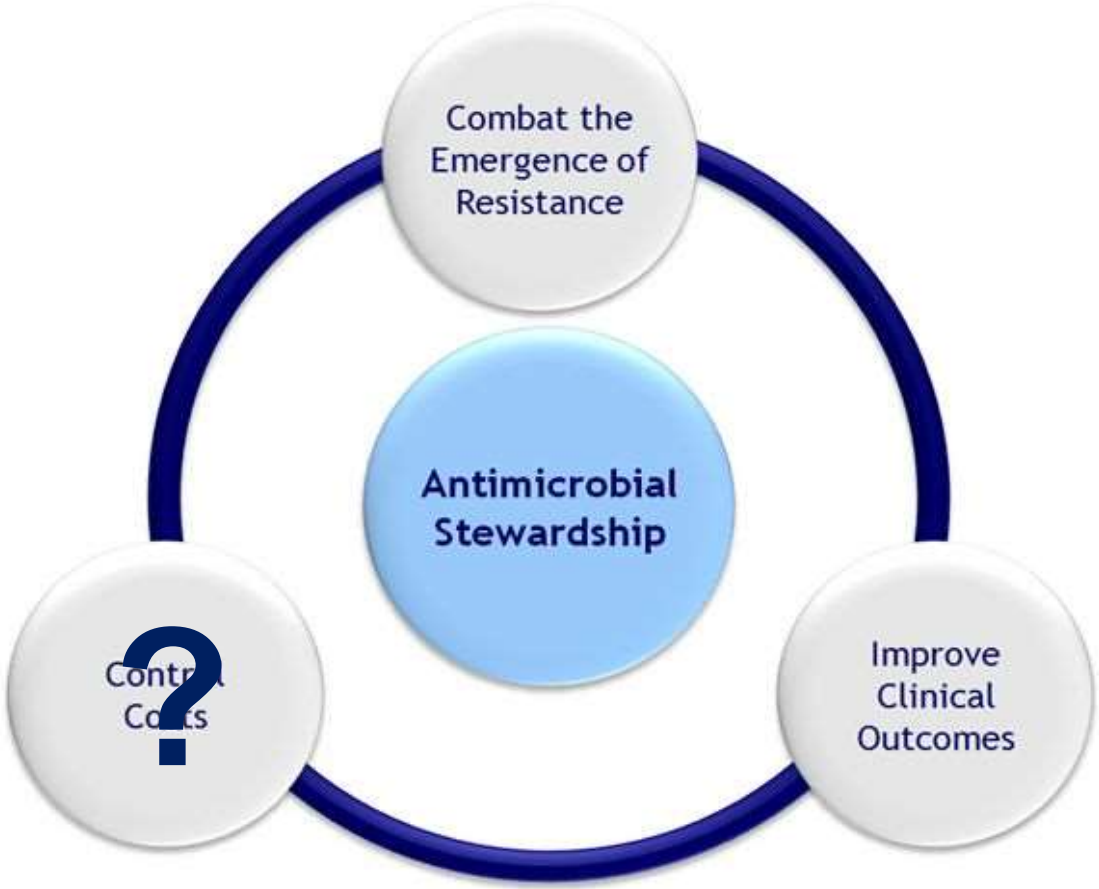
What is antimicrobial stewardship (AS)?

"Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration".

Goals of Antimicrobial Stewardship[1]



1. Lawrence KL, Kollef MH. *Am J Respir Crit Care Med.* 2009;179:434-438.

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Actions to optimize antimicrobial use in the veterinary sector

Guardabassi et al. 2018

- Reduce overall antimicrobial consumption
  - Ban of growth promoters
  - Restricted prophylaxis and metaphylaxis (not ban)
- Improve use of diagnostic testing
  - Increased use of cytology, culture and AST
  - Improved quality of microbiology diagnostic services
  - Faster and cheaper testing (Point-of-care tests)
- Prudent/restricted use of second line CIAs
- Optimize dosage regimens
  - Improved dose, administration interval and treatment duration

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Antimicrobial Stewardship in Small Animal Veterinary Practice: From Theory to Practice

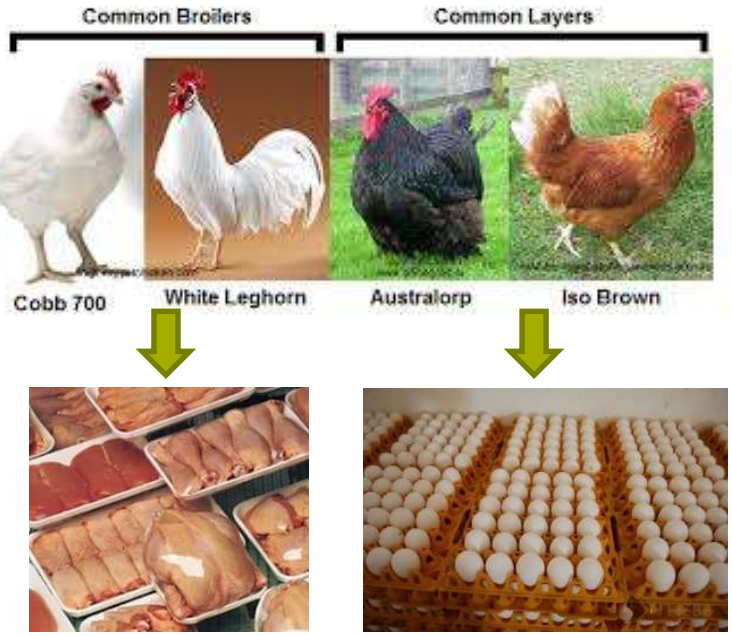
Luca Guardabassi, DVM, PhD[a,*], John F. Prescott, VetMB, DVM, PhD[b]

"Antimicrobial stewardship is perceived in the veterinary sector in a slightly different way compared with human medicine. It is generally associated with country-wide surveillance and interventions, whereas in human medicine, this term generally refers to specific programs or series of interventions to monitor and direct antimicrobial use at the hospital level"

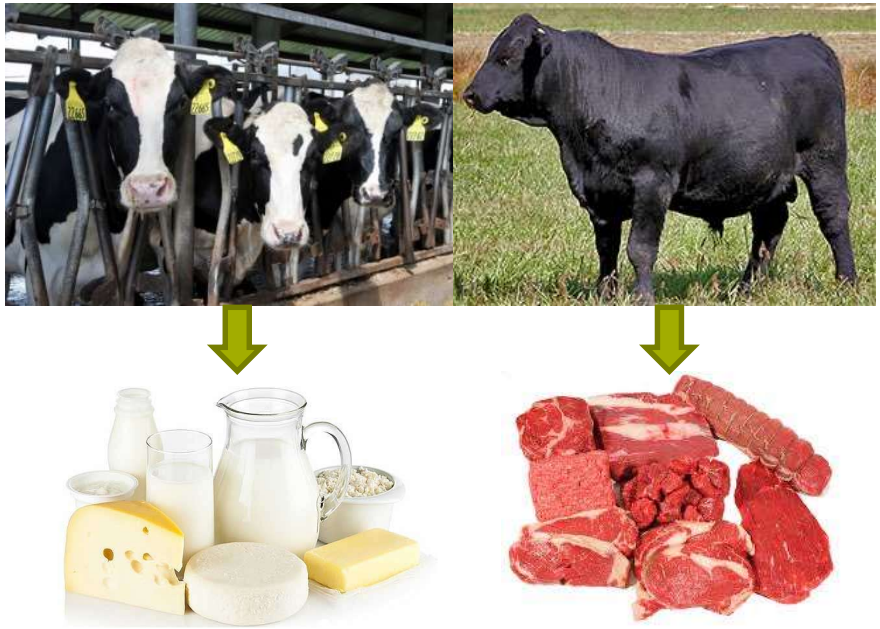
More diversity than in human medicine

Diverse species, breeds and production systems

Meat vs egg chickens



Dairy vs beef cattle



Species/sector-specific measures are required for implementating AS in veterinary medicine

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Why in livestock?

- Increasing evidence that certain MDR bacterial infections in humans are at least in part be attributable to contaminated food (ESBL-producing *E. coli*) or direct exposure to animals (LA-MRSA)
- Increasing consumer demand and governmental pressure to reduce antimicrobial use
- Benchmarking is a very effective tool to reduce antimicrobial use but how much can antimicrobial use be reduced without impacting animal welfare and AMR selection due to under-treatment?

Why in companion animals?

- MDR infections that are difficult to manage with veterinary drugs are increasingly reported, inducing veterinarians to use important drugs for human use
- The alternative therapeutic options consist of older drugs (e.g. rifampicin and chloramphenicol) that are not always effective and have significant side effects and drawbacks
- Critically important antimicrobials (CIAs) such as third generation cephalosporins and fluoroquinolones are widely used. How much should the use of these drugs be restricted to manage infections in our 'best friends'?

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Critically important antimicrobials (CIAs)

Class	Antibiotic	OIE 2015	WHO 2016	EU (EMA, ECDC, EFSA)
	Penicillins G, M	Critical	Critical	Cat.1 low risk
	Amoxicillin (penicillin A)			Cat. 2 high risk
	Anti-staph penicillin, (di)cloxacillin, oxacillin, nafcillin		Very important	Not evaluated
	Carbapenems, monobactams, other penems	unavailable	Critical	Cat. 3. Prohibited
	1st/2nd generation cephalosporins	Very important	Very important	Not evaluated
	3rd/4th generation cephalosporins	Critical priority	Critical priority	Cat. 2 Very high risk
	Quinolones (flumequin)	Very important		
	'-Oxacin' fluoroquinolones	Critical priority		
	Aminoglycosides	Critical	Critical	Cat. 2 High risk
	Aminocyclitols, spectinomycin		important	Not evaluated
	Tetracyclins		Very important	Cat. 1 low risk
	Mactrolides		Critical priority	
	Lincosamides, lincomycin, clindamycin	very important	Very important	Not evaluated
	Pleuromutilins, tiamulin		Important	
	Streptogramins, virginiamycin	important	Very important	
	Sulfamides +/- trimethoprim	Critical		
	Sulfones, dapsone	not listed		
	Phenicols (chloramphenicol, florfenicol)	Critical		
	Polypeptides, polymyxins (colistin)	Very important	Critical priority	Cat. 2 Very high risk
	Other polypeptides (bacitracin)		Important	Not evaluated
	Fusidic acid	important	Very important	
	Rifamycin, ansamysins	Very important	Critical	Cat. 1 Low risk
	Glycylglycin (tigecycline), lipopeptides, oxazolidinones	unavailable		Cat. 3 prohibited
	Glycopeptides		Critical priority	
	Phosphonic acide, fosfomycin	Very important	Critical	
	Nitrofurans, **nitromidazoles**	not listed	important	Not evaluated
	Ionophores	Very important	not listed	
	Aminocoumarins, novodbiocin, Orthosomycins, avilamycin, phosphoglycolipids, flavomycin, quinoxalins, carbadox…	Important		

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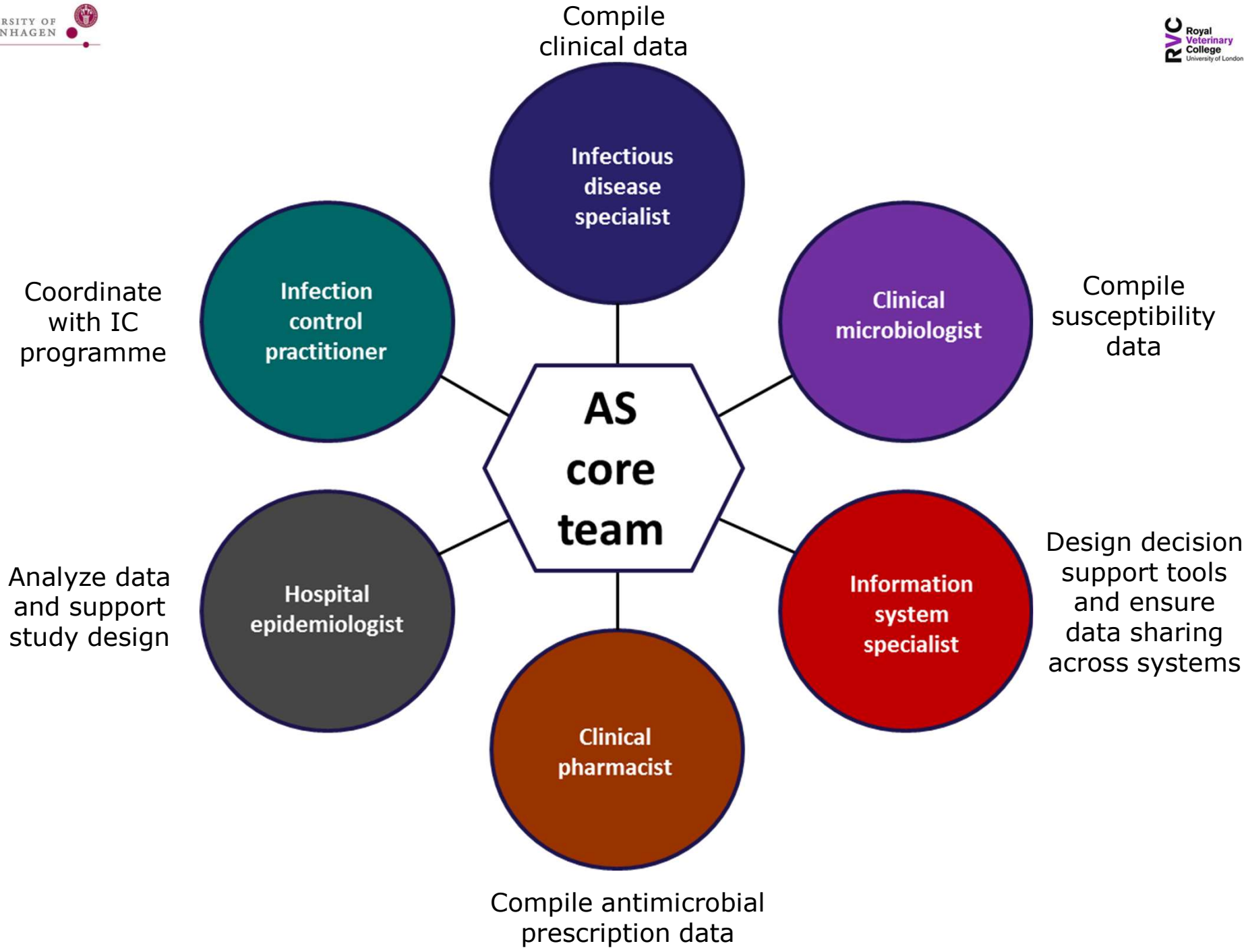
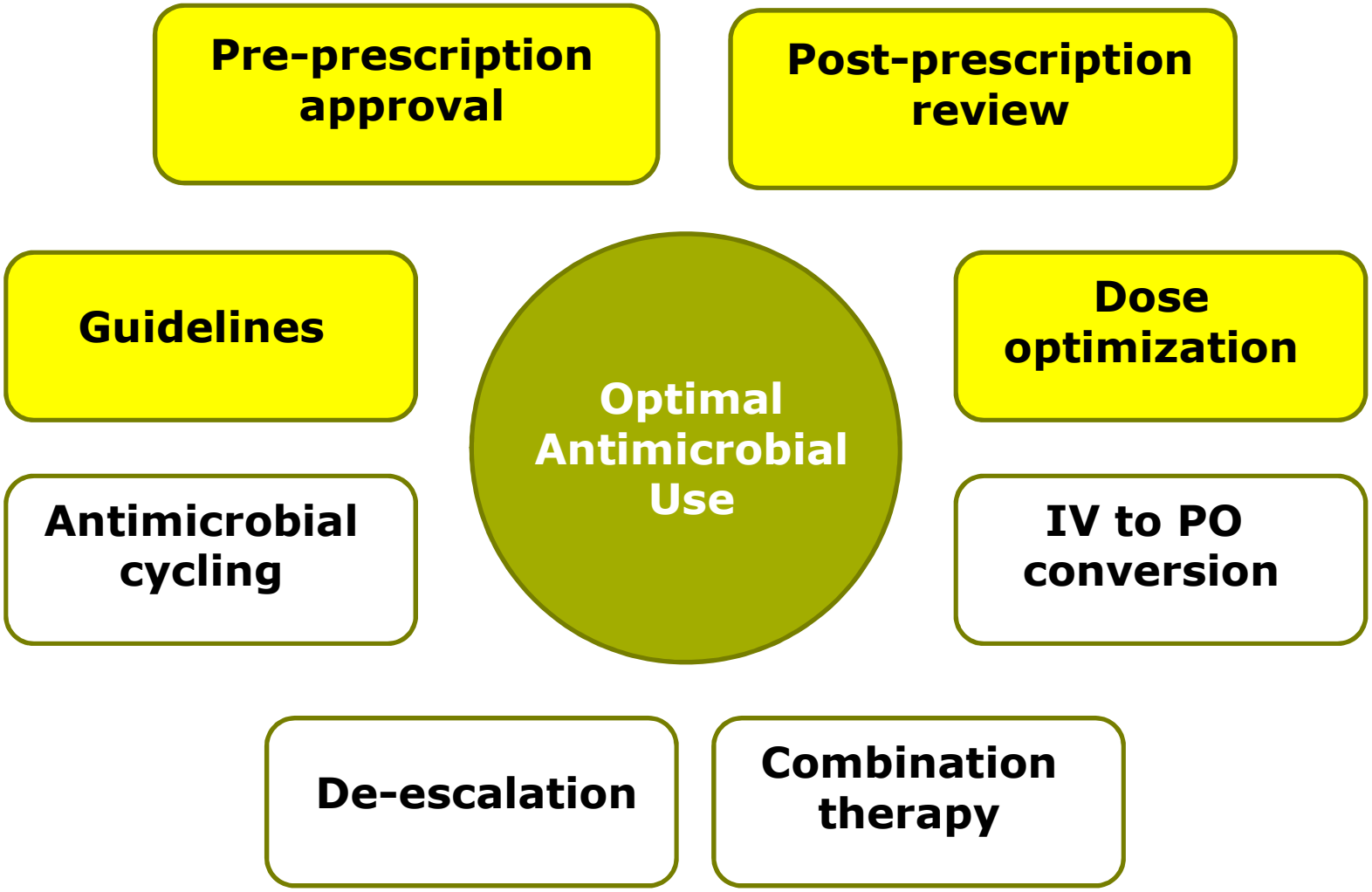
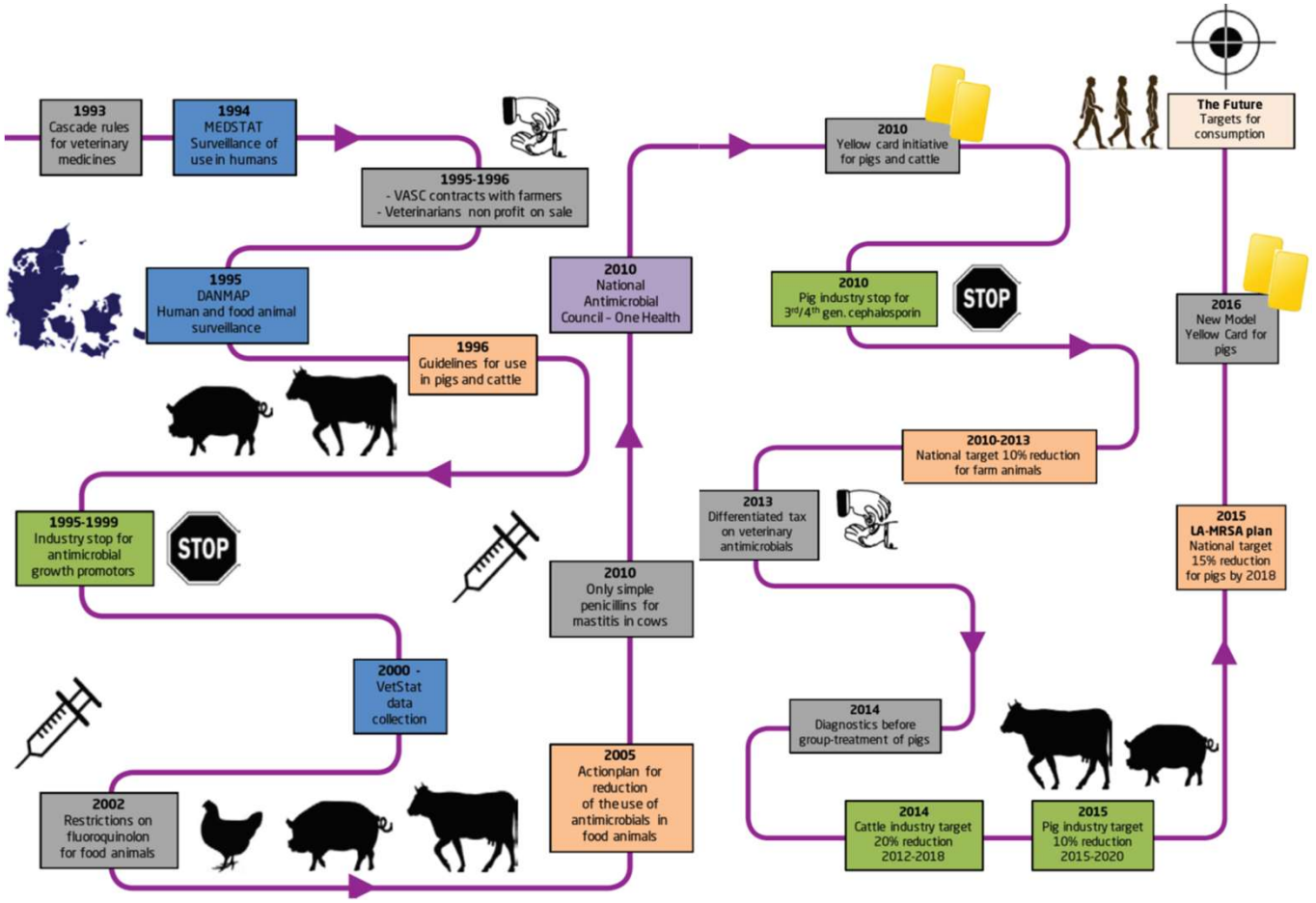

Compile clinical data
Infectious disease specialist
Coordinate with IC programme
Infection control practitioner
Clinical microbiologist
Compile susceptibility data
AS core team
Analyze data and support study design
Hospital epidemiologist
Information system specialist
Design decision support tools and ensure data sharing across systems
Clinical pharmacist
Compile antimicrobial prescription data

AS strategies in human hospitals



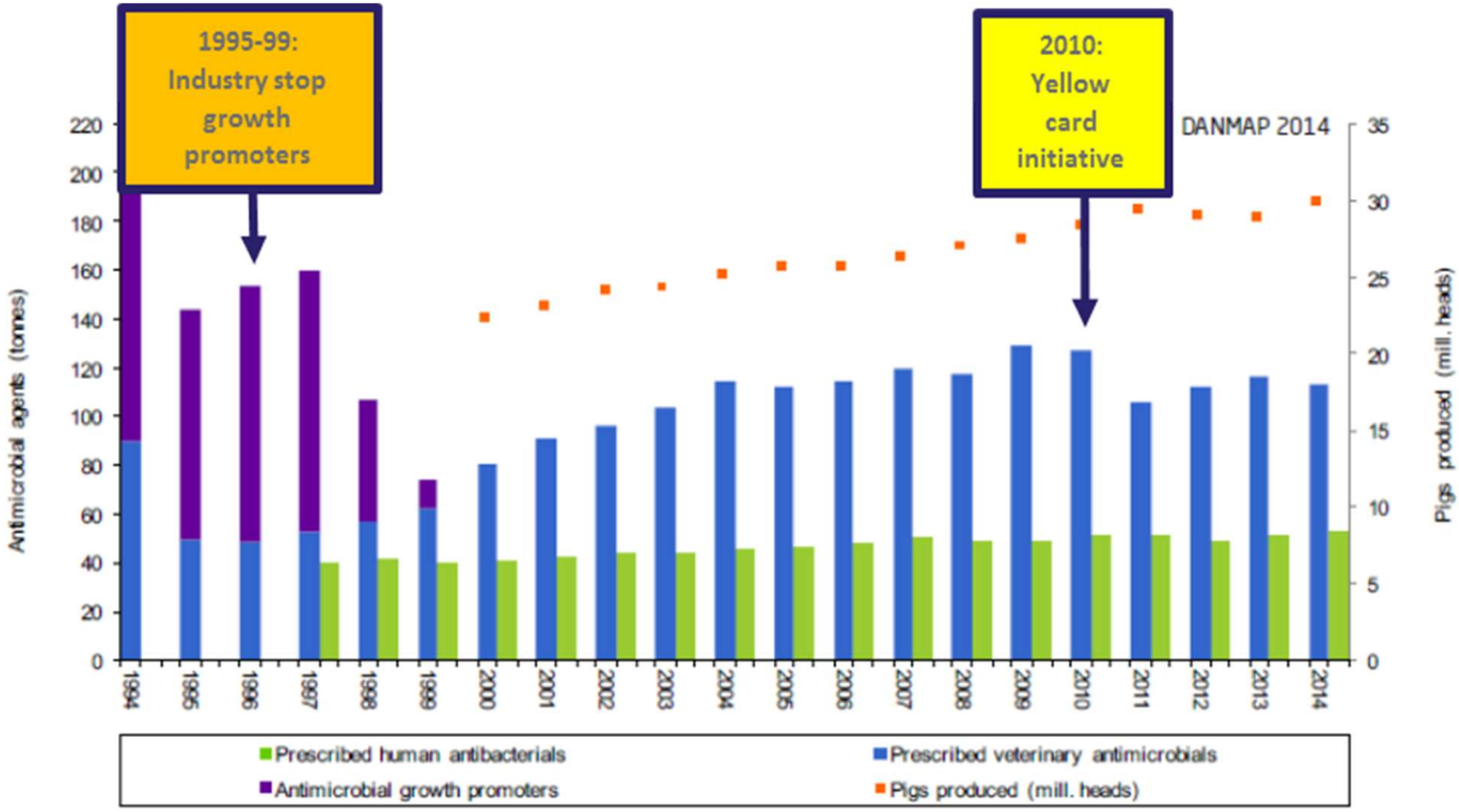
AS in Denmark

DANMAP 2015 www.danmap.org



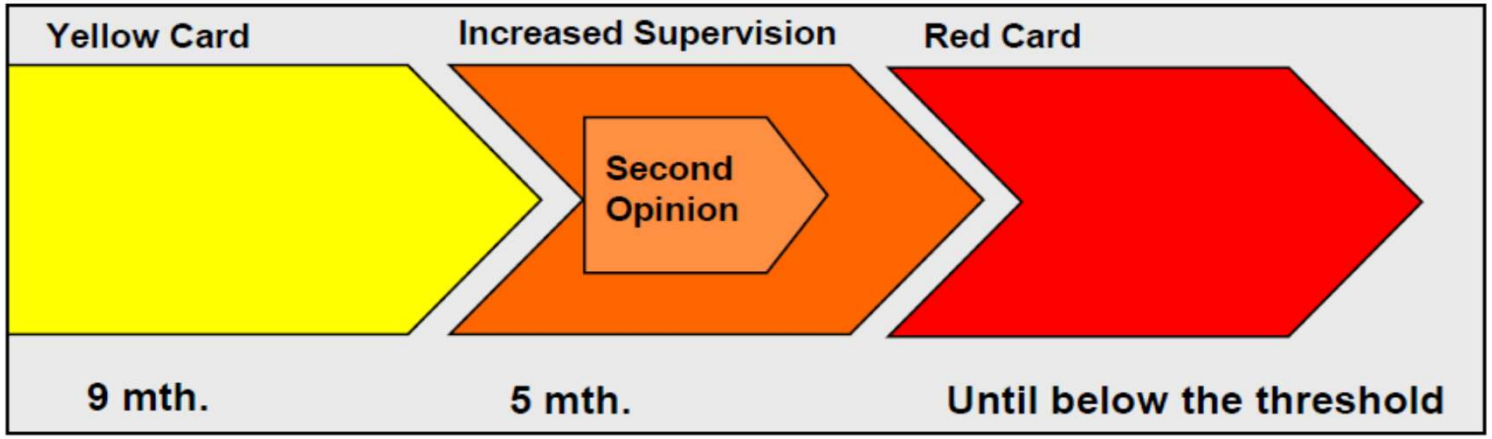
Effects of AS interventions in DK, 1994-2014

DANMAP 2014 (www.danmap.org)



The ‘yellow card’ initiative

Each year the DVFA will issue thresholds for antibiotic consumption in different age groups of pigs and cattle. The yellow card rule is activated If the average antibiotic consumption in a holding within a nine month period exceeds one of the thresholds.



Yellow card. First injunction compelling the owner of the holding to reduce the antibiotic consumption in the holding below the maximum limits within 9 months of the issuance of the injunction.

Increased supervision. Second injunction compelling the farm owner to seek expert advice from an impartial veterinarian providing an action plan to reduce antibiotic consumption below the maximum limits within 5 months.

Red card. Third injunction compelling the farm owner to implement action plan or – as a last resort – to reduce the stocking density with a suitable percentage to ensure that the consumption is reduced to a level below the threshold levels.

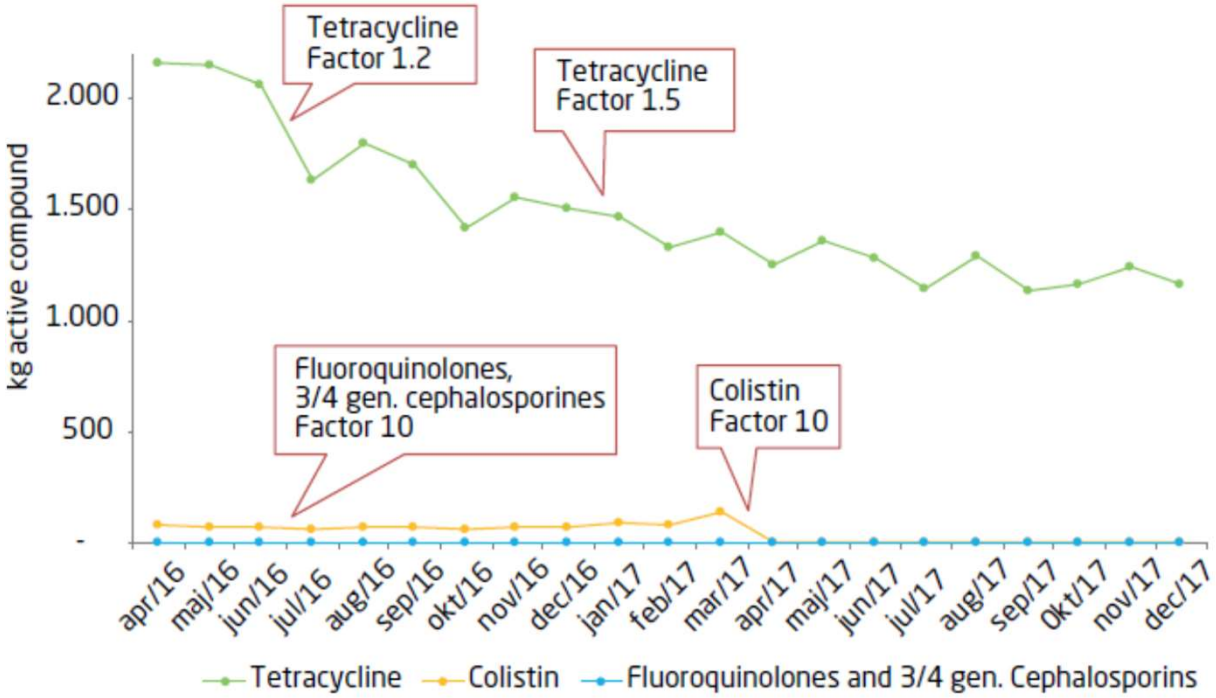
The farm owner has to pay a fee for each injunction and for all inspection visits, including the costs of the expert advice

Effects of the differentiated Yellow Card initiative

DANMAP 2017 (www.danmap.org)

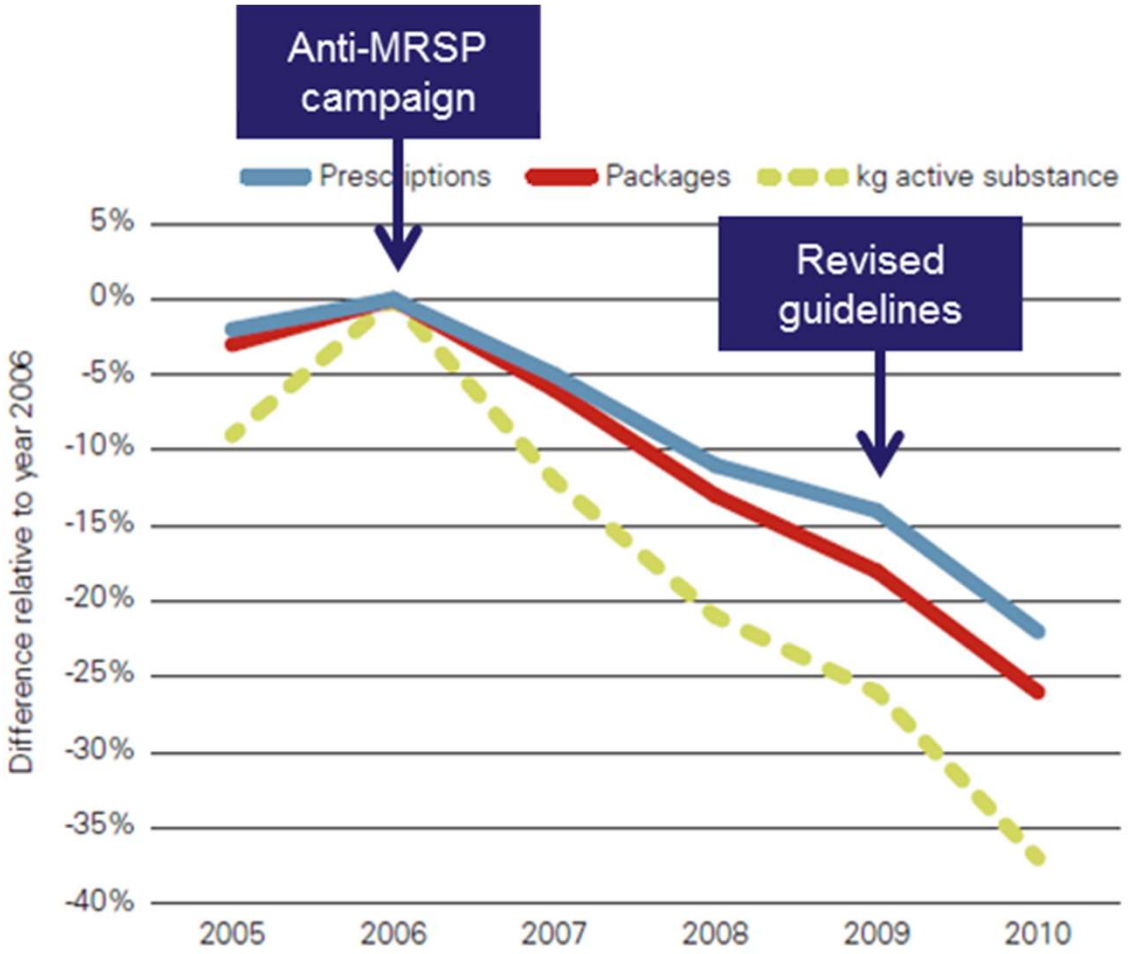
In 2016, DVFA further developed the Yellow Card by including a multiplication factors to adjust the amount used of some target antimicrobials. The goal is to discourage/reduce the use of these antimicrobials.

Figure 1 Use of selected antimicrobial agents in pigs per month (from april 2016), Denmark



AS interventions in companion animals in Sweden

Data from National Veterinary Institute (www.sva.se)



Why are guidelines important?

- An antimicrobial stewardship programme cannot be established without an antimicrobial guideline in place.
- Guidelines have been proved to be effective interventions to support clinical decision-making and change prescriber's behaviors in human medicine.
- They provide support to veterinarians who have to accomplish the reduction targets planned in their countries without impacting animal health and welfare.

Existing national guidelines

Food-producing animals	Companion animals
Denmark (in Danish ☹)	Sweden (in English ☺)
Netherlands (in Dutch ☹)	Denmark (in English ☺)
	Norway (in English ☺)
	Netherlands (in Dutch ☹)
	Australia (in English ☺)

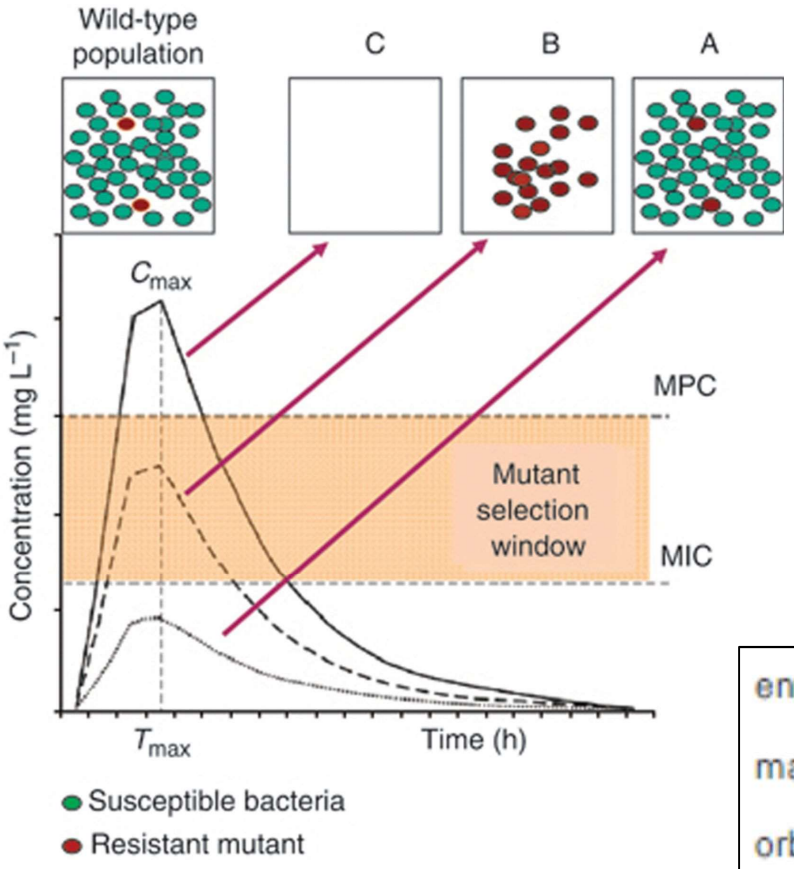
N.B. International disease-specific guidelines are only available for companion animals:

- ISCAID guidelines on skin, urinary tract and respiratory infections (open access, see www.iscaid.org ☺)
- CEVA Gram book (no open access ☹)

Challenges in veterinary AS

- Clinical practice guidelines are missing in most countries
- The individual drug intake is unknown in herd treatment (metaphylaxis)
- Lack of scientific evidence to make informed decision for development of evidence-based guidelines
- Lack of AS experts in the veterinary sector
- Poor education of veterinary students on topics related to AMR and antimicrobial students
- Limited use and quality of microbiology diagnostic services
- Conflicts of interest associated with antimicrobial prescription and dispensation

Are we using the right dose?



In conclusion, this is the first report on MPC of various fluoroquinolones against *S. pseudintermedius* isolates from dogs. Based on these results, the highest doses within the clinically recommended dose ranges of ciprofloxacin, enrofloxacin and marbofloxacin could minimize the selection of resistant mutants *in vitro*, whereas the possibility of selecting mutants with the currently used clinical doses of difloxacin and orbifloxacin, and the lowest doses within the clinically recommended dose ranges of all fluoroquinolones, seems high. Target mutations in *gyrA*-84 and *grlA*-80 contribute

enrofloxacin	5–20 mg/kg once daily
marbofloxacin	2.75–5.5 mg/kg p.o. once daily
orbifloxacin	7.5 mg/kg p.o. once daily

Awji et al. *Vet Dermatol* 2012

Are we using the right treatment duration?

BMJ 2017;358:j3418 doi: 10.1136/bmj.j3418 (Published 2017 July 26)

ANALYSIS

The antibiotic course has had its day

With little evidence that failing to complete a prescribed antibiotic course contributes to antibiotic resistance, it's time for policy makers, educators, and doctors to drop this message, argue **Martin Llewelyn and colleagues**

Martin J Llewelyn *professor of infectious diseases*[1 2], Jennifer M Fitzpatrick *specialist registrar in infection*[2], Elizabeth Darwin *project manager*[3], SarahTonkin-Crine *health psychologist*[4], Cliff Gorton *retired building surveyor*[5], John Paul *consultant in microbiology*[6], Tim E A Peto *professor of infectious diseases*[7], Lucy Yardley *professor of health psychology*[8], Susan Hopkins *consultant in infectious diseases and microbiology*[9], Ann Sarah Walker *professor of medical statistics and epidemiology*[3]

Research needs

- **Clinical trials** comparing the effects of different drugs, drug formulations, doses, administration forms and treatment durations on clinical efficacy and AMR selection
- **Cheap and fast Point-of-Care (PoC) tests** that facilitate discrimination between viral and bacterial disease, or detection of resistance to first line antimicrobials
- **Innovative pharmaceuticals** (vaccines, new antimicrobials and alternative treatments) that i) replace or minimize the use of antimicrobials that are being phase out in livestock (colistin and zinc oxide) or ii) meet the demand for management of MDR infections in companion animals

Educational needs

- **Training of a new generation of antimicrobial stewards** that can provide veterinary students and practitioners with up-to-date education on AMR and antimicrobial use in all countries
- **Development of evidence-based international guidelines** that set the basis for the development and harmonization of national treatment guidelines
- **Development of national guidelines** that take into consideration local patterns of antimicrobial use and AMR, drug availability in the market, specificities of national livestock production systems as well as cultural and regulatory differences between countries

Take-home messages

- Some countries (like Denmark) have provided evidence that centralized AS interventions drastically reduce antimicrobial use in livestock – the other countries should follow the example
- AS programmes at the clinic/farm level are a largely unexplored approach to improve antimicrobial use in function of the local needs and requirements
- Investments in "constructive" research and education are needed to fully implement AS and effectively tackle AMR beyond a mere reduction of antimicrobial consumption

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ESGVM ESCMID STUDY GROUP FOR VETERINARY MICROBIOLOGY
European Society of Clinical Microbiology and Infectious Diseases

Royal Veterinary College University of London

ESGVM activities to promote AS

- **Position papers** on quality standards for veterinary clinical microbiology (Guardabassi et al. *Vet Dermatol* 2017) and indication patterns of antimicrobial use in animals (submitted to JAC)
- **Courses on antimicrobial stewardship** in small animal veterinary medicine in Gothenburg in 2018 and in Birmingham in 2018
- **Surveys** to evaluate veterinary education on AMR and antibiotic use in the EU (PREPARE-VET)
- **Clinical practice guidelines** on treatment of key diseases for which guidelines are lacking:
  - SSI and gastroenteritis in small animals (2019)
  - Respiratory infections in cattle (2019)
  - Post-weaning enteritis in pigs (2020)

Course in Gothenburg in 2016


Course in Birmingham in 2018

ESCMID ICOHAR

International Conference on One Health Antimicrobial Resistance

Utrecht 16-18 April 2019

ESCMID ICOHAR is a truly One Health conference focusing on transfer of AMR at the interface between humans, animals and the environment as well as on the numerous AMR-related challenges shared by clinicians, clinical microbiologists, infectious disease specialists and researchers working in human and veterinary medicine (e.g. control of AMR outbreaks, harmonization of antimicrobial susceptibility testing, implementation of antimicrobial stewardship, development alternatives to antimicrobials, etc).

Thank you!

For more info and registration:

www.icohar2019.org