Antimicrobial resistance and antimicrobial use in veterinary medicine

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Public health

- Resistance influenced by both human and non-human antimicrobial usage and exposure
- Antimicrobial resistance in various commensals in animals and/or zoonotic pathogens
  - Food borne, direct contact or environmental transmission
    - MRSA: livestock and workers, dogs and owners
    - Extended spectrum β-lactamase (ESBL) producing *E. coli*
    - *Campylobacter*
    - *Salmonella*
    - *Pseudomonas*
    - *Colistin (plasmid borne)*




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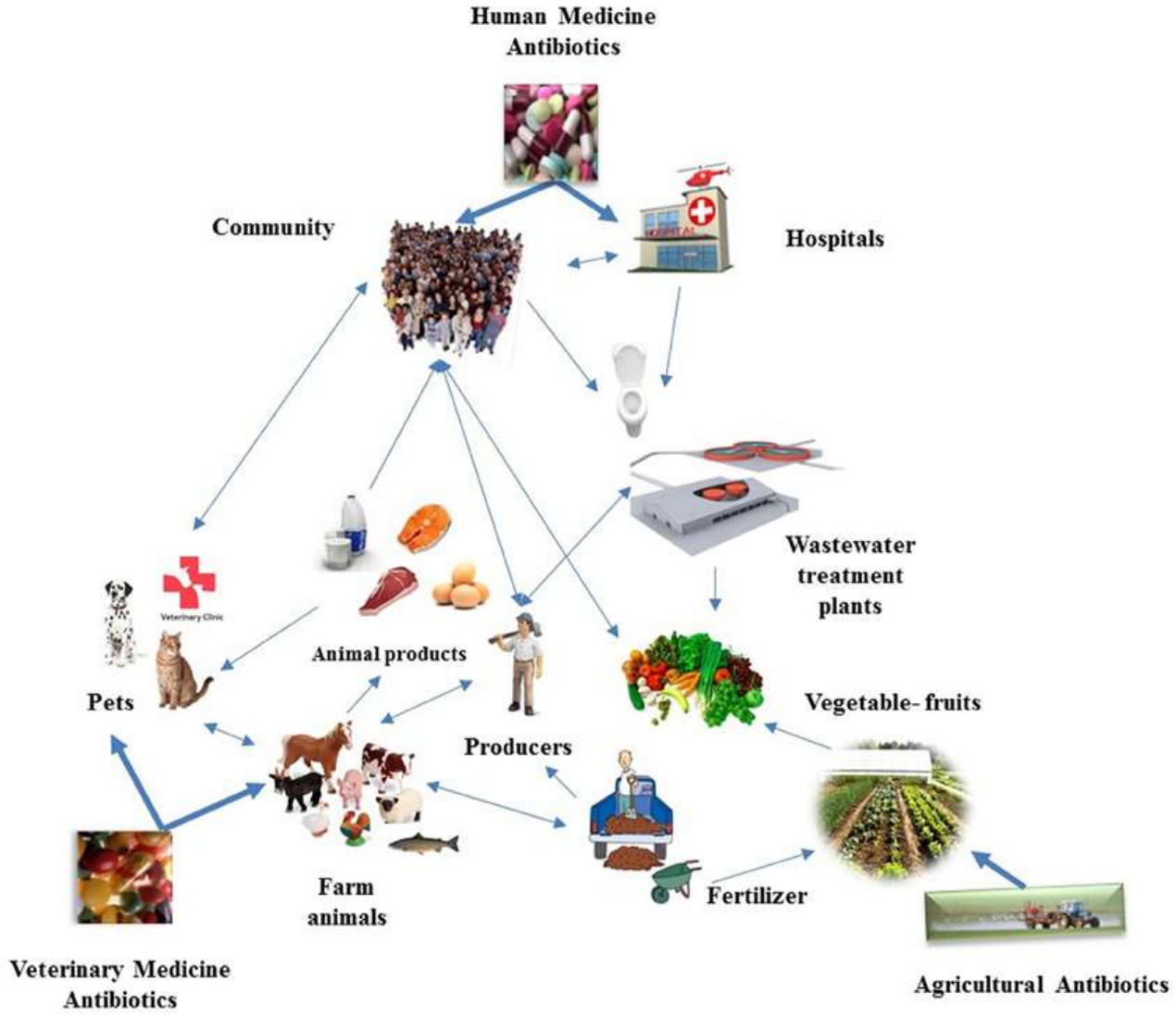
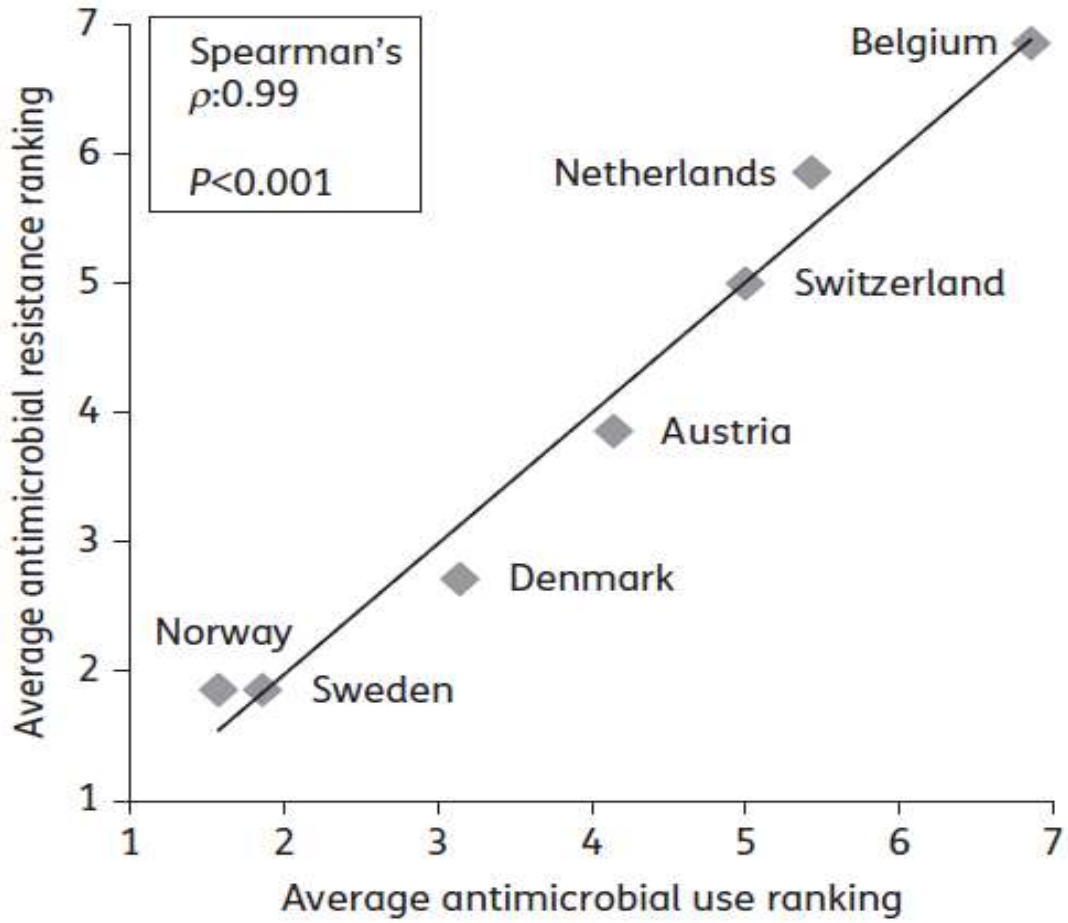
Ecology of AMR



Linking antimicrobial use to antimicrobial resistance in 7 EU countries based on monitoring data



Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: a report on seven countries.
Chantziaras et al., 2013

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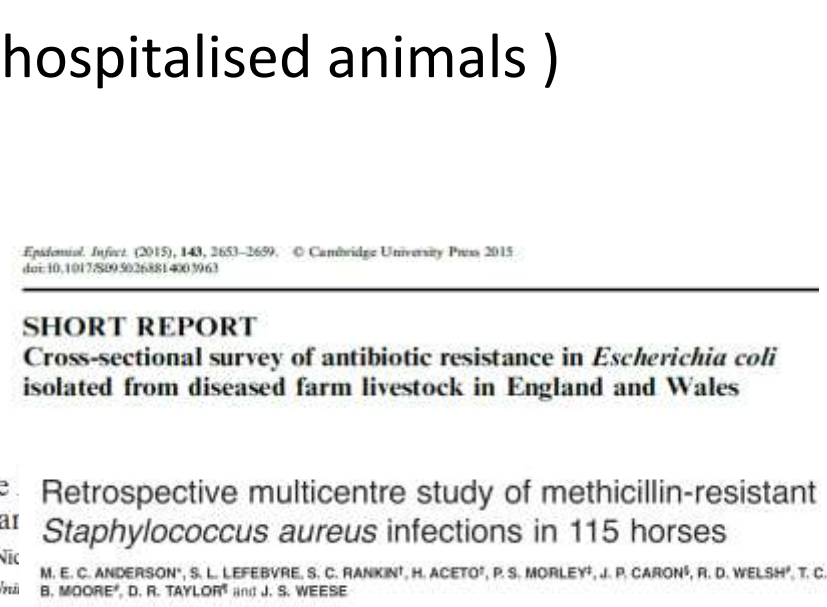
Animal health

- Resistant infections in animals
  - ESBL *E. coli* - emerging threat?
    - *Infections in dogs and cats - urinary tract etc.*
  - Multidrug resistant *Enterotoxigenic E. coli lambs*
  - Multidrug resistance *E. coli* pigs
  - Multidrug swine dysentery
  - MRSA infections (hospitalised animals)



Epidemiol. Infect. (2015), **143**, 2653–2659. © Cambridge University Press 2015
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SHORT REPORT

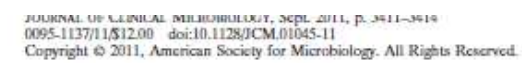
Cross-sectional survey of antibiotic resistance in *Escherichia coli* isolated from diseased farm livestock in England and Wales

ANTIMICROBIAL RESISTANCE

Multidrug resistance in enterotoxigenic K99 *E coli* infection in lambs

WE would like to report a neonatal lamb scour investigation in which multi-antibiotic resistant enterotoxigenic *Escherichia coli* with K99 antigen (ETEC K99) isolates were detected in a commercial sheep flock, to illustrate to practitioners that it cannot be assumed that commonly used antibiotic preparations will be effective. The Veterinary Medicines Directorate (VMD) collates laboratory submissions (culture and sensitivity) from the APHA and has previously found that multiresistant *E coli* isolates were increasing, and accounted

52 | Veterinary Record | July 11, 2015



JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 2011, p. 3411–3414
0095-1137/11/$12.00 doi:10.1128/JCM.01045-11
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Detection of Extended-Spectrum-β-Lactamase-Positive
in Bile Isolates from Two Dogs with Bacterial Cholar

Dorina Timofte,* Julien Dandrieux, Andrew Wattret, Jenny Fick, and Nic

School of Veterinary Science, University of Liverpool, Leahurst Campus, Cheshire, Uni

Retrospective multicentre study of methicillin-resistant *Staphylococcus aureus* infections in 115 horses

M. E. C. ANDERSON[a], S. L. LEFEBVRE, S. C. RANKIN[b], H. ACETO[c], P. S. MORLEY[d], J. P. CARON[e], R. D. WELSH[a], T. C. HOLBROOK[a], B. MOORE[a], D. R. TAYLOR[a] and J. S. WEESE

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Reducing/optimising antimicrobial use in animals

- Restriction or banning use of the critically important antimicro animals (fluoroquinolones etc)
- Threat of separating prescribing and dispensing
- Restriction of prophylactic antimicrobials
  - In feed
  - Dry cow therapy
- Banning use as growth promoter (outside EU)
- Data collection
  - How much antimicrobials should be used?
  - Benchmarking – farms, countries!
- Economics of food production
- Animal welfare
- Internationally - lack of data, legislation. AM use crossover between human-animal.

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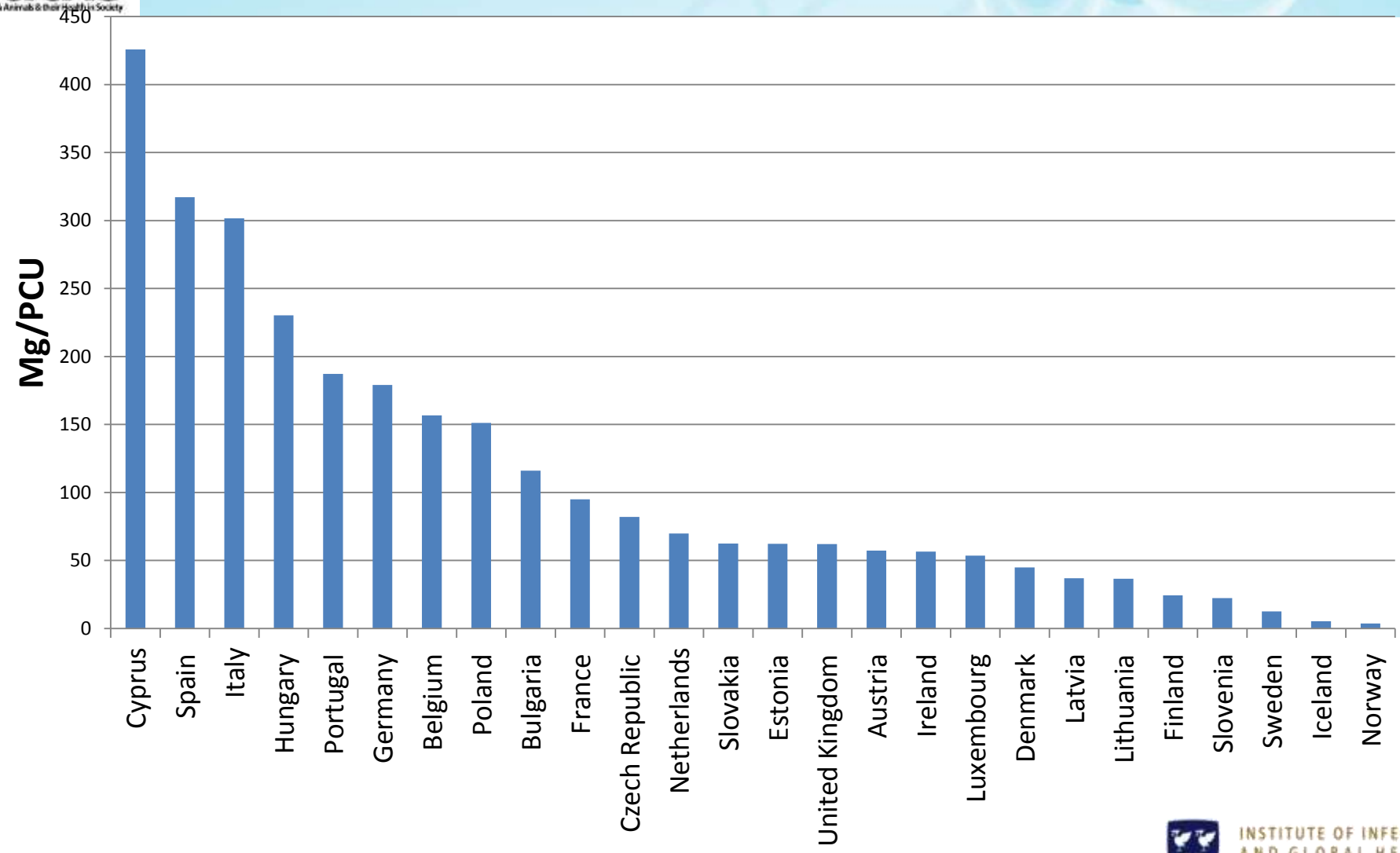
Collection of antimicrobial **sales** data across EU/EEA Countries

- The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)
  - data on the sales of veterinary antimicrobials from 26 EU/EEA countries
- Data limitations
  - Sales data only
  - Many antimicrobial products authorised for use in multiple species
  - Major species differences in usages
  - Not actual on farm use

Sales of antimicrobials for food-producing animals in mg/PCU, 2013

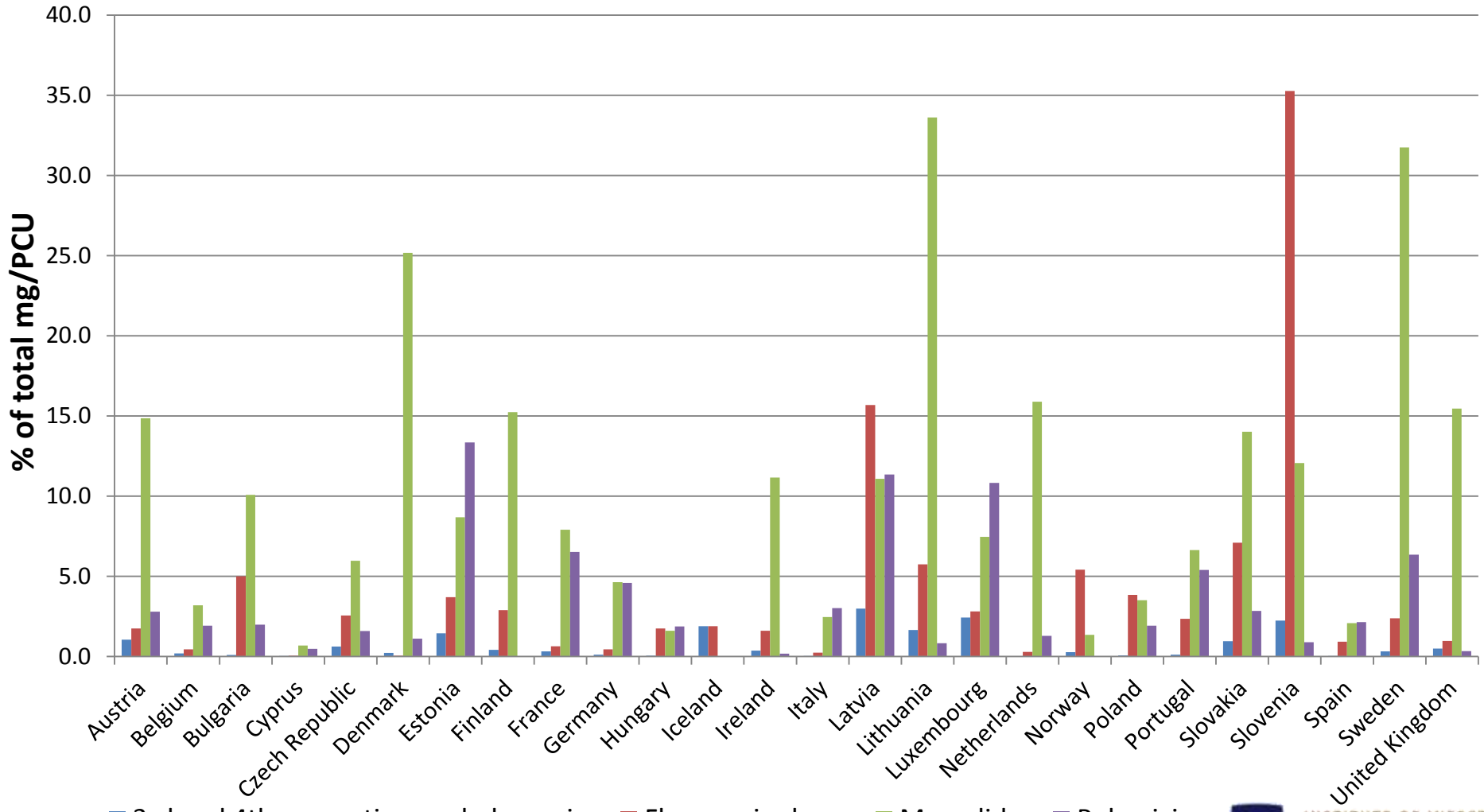


Source – ESVAC, 2015

NB – Food producing animals includes horses

Sales of critically important antimicrobials for food-producing animals in mg/PCU, by country, for 2013

Source – ESVAC, 2015



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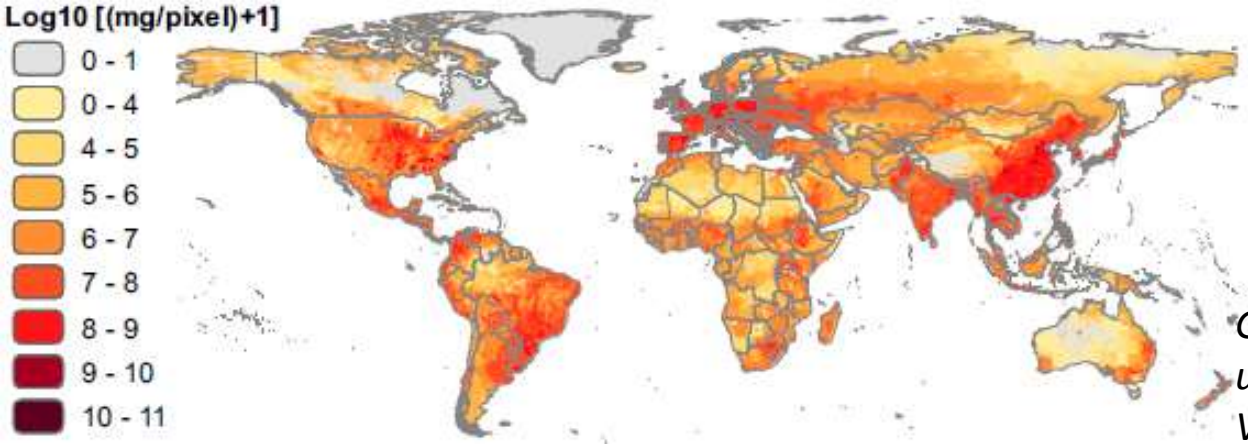
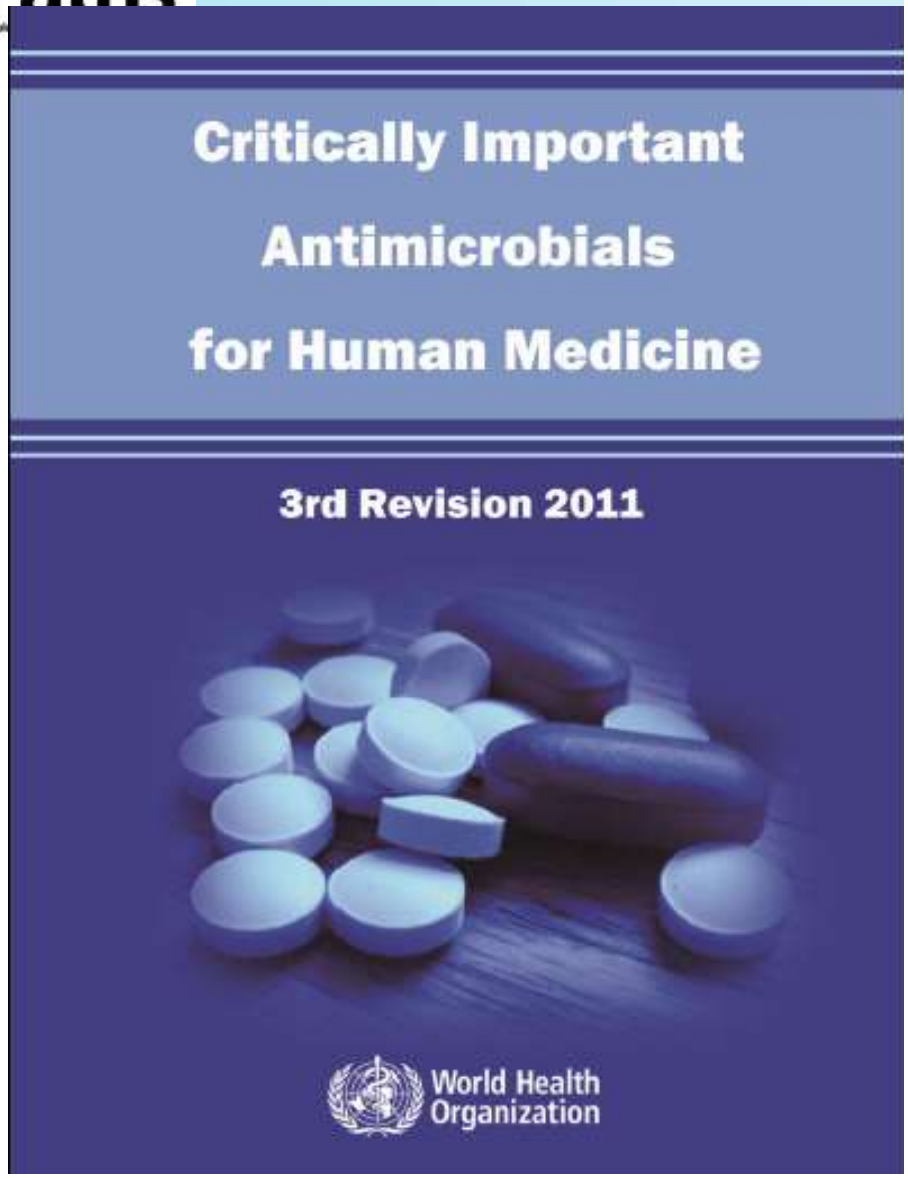
Global consumption of antimicrobials in food animal production

- Estimated at 63,151 tons in 2010
- Projected rise by 67%, to 105,596 tons, by 2030.
  - Two thirds of increase due to the growing number of animals raised for food production.
  - third is imputable to a shift in farming practices, to be intensive farming



Global trends in antimicrobial use in food animals
Van Boeckel et al 2015.PNAS

WHO - protecting public health



7. Highest Priority Critically Important Antimicrobials

These are the classes of drugs that met all three priorities (1.1, 1.2 and 2.1): Fluoroquinolones, 3rd and 4th generation cephalosporins, Macrolides, and Glycopeptides.

Fluoroquinolones are known to select for fluoroquinolone-resistant *Salmonella* spp. and *E.coli* in animals. At the same time, fluoroquinolones are one of few available therapies for serious *Salmonella* spp. and *E.coli* infections. Given the high incidence of human disease due to *Salmonella* spp. and *E. coli*, the absolute number of serious cases is substantial.

3rd and 4th generation cephalosporins are known to select for cephalosporin-resistant *Salmonella* spp. and *E. coli* in animals. At the same time, 3rd and 4th generation cephalosporins are one of few available therapies for serious Salmonella and *E. coli* infections, particularly in children. Given the high incidence of human disease due to *Salmonella* spp. and *E. coli*, the absolute number of serious cases is substantial.

Macrolides are known to select for macrolide-resistant *Campylobacter* spp. in animals, especially *Campylobacter jejuni* in poultry. At the same time, macrolides are one of few available therapies for serious campylobacter infections, particularly in children, in whom quinolones are not recommended for treatment. Given the high incidence of human disease due to *Campylobacter* spp., especially *Campylobacter jejuni*, the absolute number of serious cases is substantial.

Glycopeptides are known to select for glycopeptides-resistant *Enterococcus* spp. in food animals (e.g., when avoparcin was used as a growth promoter, vancomycin resistant enterococcus (VRE) developed in food animals and were transmitted to people). At the same time, glycopeptides are one of the few available therapies for serious enterococcal infections. Given the high number of cases, the previously documented occurrence of transmission of VRE to people from food animals and the very serious consequences of treatment failures in such cases, this class was re-classified as being of highest priority in the 3rd revision of the List.

International and national responsible use initiatives

Paths

antibacterials

Are you PROTECTing your antibacterials?

Write your practice policy on empirical antibacterial use in the boxes below

Periodontal disease

amoxicillin OR amoxicillin/clavulanate OR ampicillin OR clindamycin OR metronidazole + spiramycin. With or without chlorhexidine mouthwash

Practice Policy:

Respiratory infections

Bacterial pneumonia (including aspiration):
- cats: amoxicillin/clavulanate OR doxycycline
- dogs: aminoglycoside* + metronidazole* OR amoxicillin + fluoroquinolone OR amoxicillin + metronidazole* OR doxycycline OR oxytetracycline

Practice Policy:

Bacterial rhinitis, chronic rhinitis and sinusitis: amoxicillin/clavulanate

Practice Policy:

Kennel cough: no antimicrobials in mild cases; more severe: amoxicillin/clavulanate OR doxycycline OR oxytetracycline.

Practice Policy:

Suspected ***Mycoplasma:***
- cats: azithromycin* OR doxycycline.
- dogs: azithromycin* OR doxycycline OR oxytetracycline.

Practice Policy:

Pyothorax:
- cats: amoxicillin/clavulanate
- dogs: ampicillin + fluoroquinolone OR clindamycin + fluoroquinolone OR metronidazole* + fluoroquinolone.

Practice Policy:

Gastrointestinal infections

Acute diarrhoea with complications: amoxicillin/clavulanate OR 1st generation cephalosporin.

Practice Policy:

Anal sacculitis: lavage plus topical instillation (saline or chlorhexidine); amoxicillin/clavulanate

Practice Policy:

Confirmed ***Campylobacter* (if clinically significant):** enrofloxacin OR erythromycin*

Practice Policy:

Cholangitis/cholangiohepatitis: amoxicillin OR amoxicillin/clavulanate OR ampicillin OR cefalexin. Metronidazole* may be added in dogs

Practice Policy:

Gastrointestinal bleeding or bacterial translocation: metronidazole* + amoxicillin/clavulanate OR metronidazole* + 1st generation cephalosporin. Add fluoroquinolone or aminoglycoside* to improve Gram -ve cover.

Practice Policy:

Suspected ***Helicobacter:*** amoxicillin + metronidazole* OR azithromycin* + tinidazole OR clarithromycin* + metronidazole*. In combination with bismuth (caution in cats) OR famotidine OR omeprazole OR ranitidine.

Practice Policy:

Genitourinary infections

Cystitis: amoxicillin/clavulanate OR trimethoprim/sulfadiazine. Many cats with cystitis do not have bacterial infections - routine antibacterials not required.

Practice Policy:

Endometritis/Pyometra: amoxicillin/clavulanate OR trimethoprim/sulfadiazine

Practice Policy:

Suspected ***Leptospira:*** ampicillin OR penicillin G; doxycycline for carriers. Aminopenicillins treat bacteraemia but do not address carrier state.

Practice Policy:

Prostatitis (acute): fluoroquinolones OR trimethoprim/sulfadiazine. Culture required in chronic cases

Practice Policy:

Pyelonephritis (acute): trimethoprim/sulfadiazine. Culture required in chronic cases

Skin infections

Bite and other traumatic wounds: Lancet, debride and lavage. In cat bites amoxicillin first choice, otherwise choice as for Pyoderma. Heavily infected/deeper injuries: metronidazole OR amoxicillin/clavulanate + fluoroquinolone are appropriate while awaiting culture results.

Practice Policy:

Infected traumatic wound: amoxicillin/clavulanate OR 1st generation cephalosporin.

Practice Policy:

Pyoderma:
Empirical choice of antibacterials suitable for surface and superficial pyoderma (if no resistance or treatment failure) but culture required for deep pyodermas.
- **Topical:** chlorhexidine AND/OR fusidic acid OR silver sulfadiazine*. (Antifungals for concurrent Malassezia often useful.)
- **Systemic:** amoxicillin/clavulanate OR cefadroxil OR cefalexin OR cefovecin (if problems expected with administration/compliance) OR clindamycin OR fluoroquinolones (if others inappropriate). Continue 1 week beyond resolution of clinical signs.

Practice Policy:

Pyoderma (idiopathic recurrent):
- **Topical therapy** important: antimicrobial shampoos/rinses, especially chlorhexidine.
- **Systemic:** Alternatives to antibacterials include immunostimulants (Staph Phage Lysate, autogenous vaccine). Last resort is pulse therapy 2-3 consecutive days/wk.

Practice Policy:

Pyoderma (confirmed MRSA/MRSP): choice based on sensitivity. If sensitivity not known, use topical chlorhexidine AND/OR fusidic acid OR systemic tetracyclines OR trimethoprim/sulfadiazine.

Practice Policy:

Pyogranuloma: as for Pyoderma but culture essential and may need to be repeated. Filamentous bacteria: clindamycin OR doxycycline OR trimethoprim/sulphonamide. Mycobacteria: fluoroquinolones + doxycycline.

Practice Policy:

Ear infections

Otitis externa (erythroceruminous):
- **Topical:** fusidic acid OR thiamphenicol* OR gentamicin OR marbofloxacin OR orbifloxacin OR polymixin B/miconazole. (Antifungals for treat concurrent Malassezia will often be useful.) Combine with effective antibacterial ear cleansers with a low pH (chlorhexidine, chlorocresol, isopropyl alcohol, PDMX.)
- **Systemic:** choice as for Pyoderma.

Practice Policy:

Otitis externa (suppurative) or otitis media:
- **Topical:** Choice (including ear cleaners) as for erythroceruminous OE. Enrofloxacin, marbofloxacin, aqueous gentamicin appear to be safe in the middle ear. Multidrug-resistant infections: 1.7% ceftazidime OR 2.8% clavulanate/ticarcillin OR 0.6% enrofloxacin OR 0.2% marbofloxacin OR 0.1- 0.5% silver sulfadiazine (diluted in tris/EDTA).
- **Systemic:** choice as for Pyoderma.

Practice Policy:

Eye infections

Bacterial conjunctivitis:
- **Topical:** cefazolin OR fusidic acid OR gentamicin.

Practice Policy:

Suspected ***Chlamydophila*:**
- **Systemic:** doxycycline OR enrofloxacin. Topical fusidic acid may be added if desired.

Practice Policy:

Miscellaneous

Endocarditis: amoxicillin/clavulanate + enrofloxacin OR amoxicillin/clavulanate + metronidazole*

Practice Policy:

Mastitis: amoxicillin/clavulanate OR trimethoprim/sulfadiazine.

Practice Policy:

Suspected ***Mycoplasma haemofelis*** (formerly *Haemobartonella*) (feline infectious anaemia): doxycycline OR fluoroquinolone.

Practice Policy:

Neutropenia: Mild: no antibacterial required. Severe but asymptomatic: trimethoprim/sulphonamide. Severe and with clinical signs: 1st generation cephalosporin + fluoroquinolone.

Practice Policy:

Septic peritonitis: amoxicillin/clavulanate OR ampicillin + cefotaxime OR ampicillin + gentamicin* OR

Surgical prophylaxis

Prophylactic antimicrobial use is not a substitute for good aseptic technique.
- Perioperative antibiosis is appropriate
  - for prolonged surgery (>1.5 hours) or surgery involving implants
  - for debilitated or immunosuppressed patients
  - where infections would be catastrophic (e.g. in CNS)
  - where there is an obvious break in asepsis
  - for all bowel surgery
  - for dental procedures where there is periodontal disease
  - for contaminated wounds or pre-existing infection
- In most cases
  - intravenous amoxicillin/clavulanate OR first-generation cephalosporin
- Where anaerobic involvement is highly likely (e.g. periodontal disease)
  - *add* or *substitute* metronidazole
- For significant bowel leakage in an otherwise metabolically stable animal:
  - combination may be most appropriate, e.g. ampicillin + aminoglycoside (e.g. gentamicin)
  - If patient volume-depleted, replace aminoglycoside with fluoroquinolone.

Practice Policy

Antibacterials not indicated unless cytology and/or culture is positive

- Cardiorespiratory
  - Chronic bronchitis/allergic airway disease
  - Aspergillosis
  - Congestive heart failure
- Urinary
  - Feline lower urinary tract disease (including struvite urolithiasis)
  - Urinary incontinence
- Gastrointestinal
  - Acute vomiting (uncomplicated)
  - Acute diarrhoea (uncomplicated)
  - Chronic gastroenteritis (unless 4-week treatment trial for antibiotic-responsive diarrhoea)
  - Pancreatitis (uncomplicated)
- Surgery
  - Routine castration and ovariohysterectomy
  - Removal of uninfected skin mass not involving major reconstruction
- Metabolic
  - Polyuria, polydipsia (unless pyogenic focus suspected)
  - Weight loss
- Skin and ears
  - Malassezia dermatitis
  - Acute non-specific pruritus, scaling, nodules, crusts, etc.

DO NOT USE

There are very strong arguments that ectomycobials with restricted use in human medicine (e.g. imipenem, linezolid, teicoplanin, vancomycin) should not be used in animals under any circumstances.

Second and Third Choice Antibacterials

These include: amikacin, 3rd generation and 4th generation cephalosporins

R educe prophylaxis
- Antibacterials are **not** a substitute for surgical asepsis
- Prophylactic antibacterials are only appropriate in a few medical cases (e.g. immunocompromised patients)

O ther options
- Reduce inappropriate antibacterial prescribing (e.g. due to client pressure, in uncomplicated viral infections or self-limiting disease) by providing symptomatic relief (e.g. analgesia, cough suppressants)
- Use cytology and culture to diagnose bacterial infection correctly
- Effective lavage and debridement of infected material reduces the need for antibacterials
- Using topical preparations reduces selection pressure on resistant intestinal flora

T ypes of bacteria and drugs
- Consider which bacteria are likely to be involved, e.g. anaerobic/aerobic, Gram +ve versus Gram -ve
- Consider the distribution and penetration of the drug
- Consider any potential side effects

E mploy narrow spectrum
- It is better to use narrow spectrum antibacterials as they limit effects on commensal bacteria
- Avoid using certain antibacterials as first line agents; only use when other agents are ineffective (ideally determined by culture and sensitivity testing)

C ulture and sensitivity
- Culture promptly when prolonged courses are likely to be needed (e.g. pyoderma, otitis externa, deep/surgical wound infection) or when empirical dosing has failed

T reat effectively

What is happening in reality?

- Are guidelines being followed?
- Are all vets prescribing responsibly?
- Are animal owners /farmers using responsibly ?
- Is resistance a real or perceived issue in veterinary medicine?
- What are the main drivers of antibacterial use?
- What role do owners/farmers have ?
- What are the barriers to changing behaviour?
- How do we sustain ‘good’ behaviour?
- What impact on animal health?
- What impact on animal productivity?

Antimicrobial Prescribing Practice by Vets in UK

- Farm animal veterinary surgeons (cattle)
  - 2.8% of practices had a written antimicrobial use policy document
  - 95.3% reported being able to dispense antimicrobials at their own discretion
  - Only 9.4% and 7.8% of vets respectively, reported that they had **not used** fluoroquinolones or cephalosporins in the last year
  - Bacterial culture and sensitivity testing
    - Only 4.7% reported frequently undertaking this

Williams N, Pinchbeck G et. al. 2010

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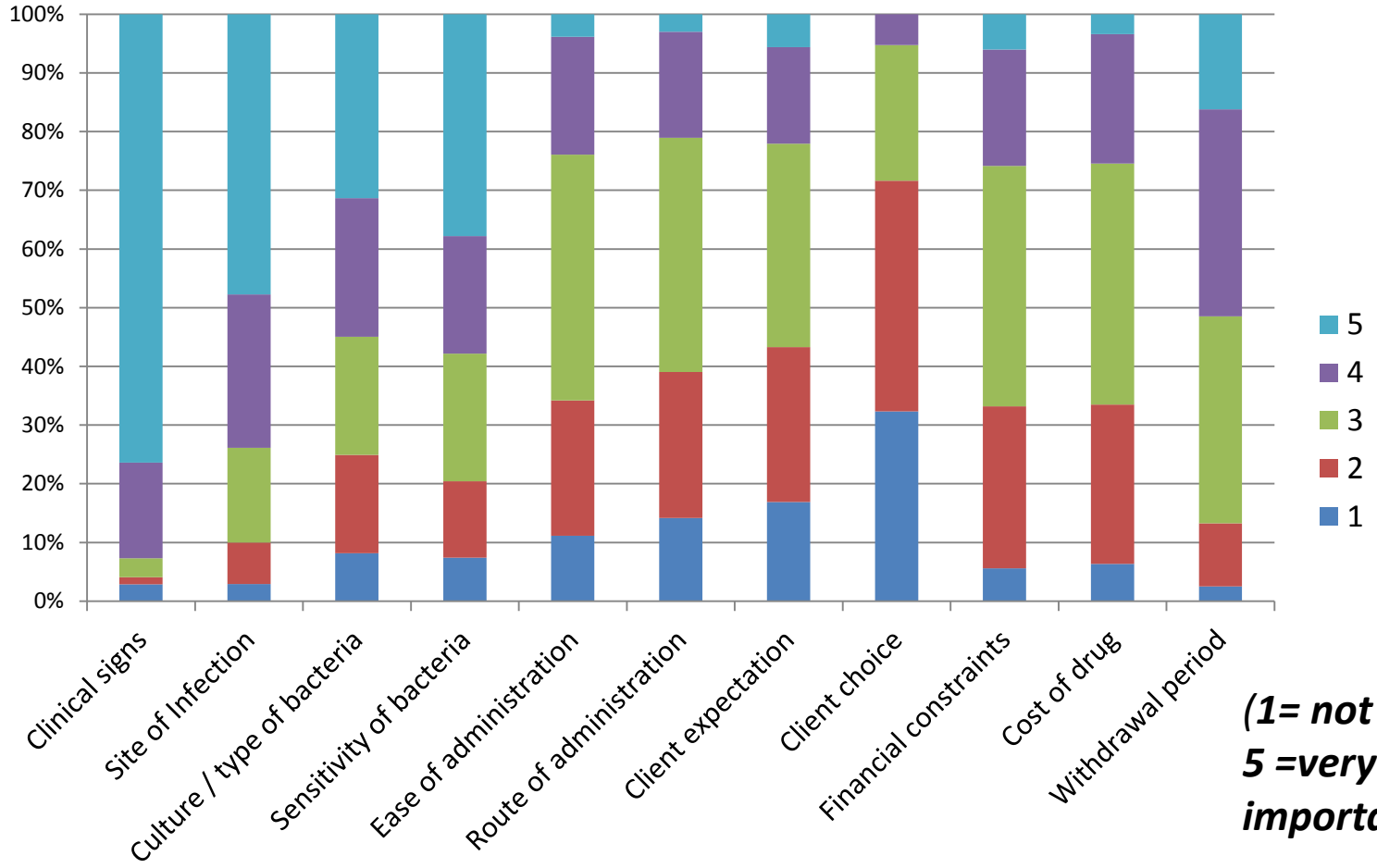
What influences choice of antibiotic for treatment of dairy cattle.



(1= not important; 5 =very important)

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Economic drivers

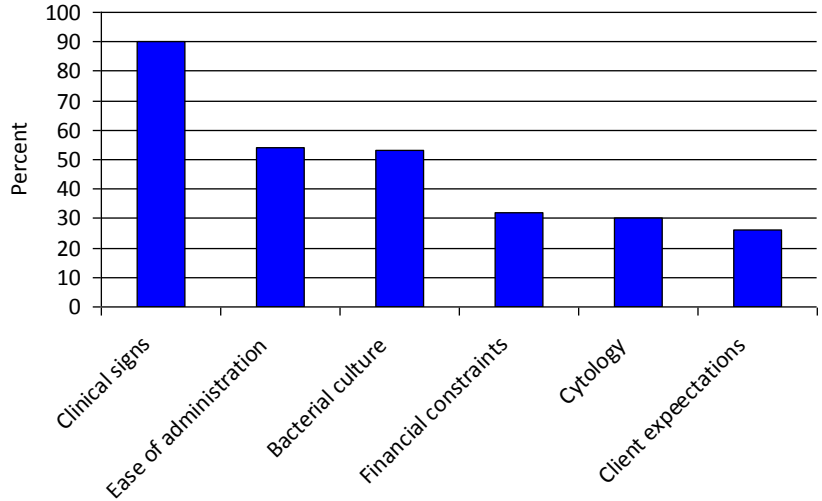
- Pen/strep €7.80 for a 3 day course for 600Kg cow
- Milk loss 4.5 days in total (3 days treatment)
- 40 litres per day x 4.5 = 180 litres = € 68.60

- 3rd gen cephalosporin 3 day course = € 16.51 course ,or one injection € 23.50.
- Convenient
- Nil milk withdrawal.

- Milk price and withdrawal times are the drivers
- Evidence for best treatment ?

Antimicrobial Prescribing Practice by Vets in UK (2010)

- Small animal animal veterinary surgeons (dogs)
  - 3.5% of practices had a written antimicrobial use policy document
  - Fluoroquinolones and 3rd generation cephalosporins .
    - 6.0% and **4.6**% of all prescriptions
    - 25.9% dogs received antimicrobials



Hughes et. al.

Drivers and motivations associated with antimicrobial prescribing practices by UK pig veterinarians and farmers

Mixed methods approach – Qualitative and quantitative

Objectives

To develop an in-depth understanding of the key drivers of prescribing and use and to determine major barriers to behaviour change

- in depths interviews with veterinarians and farmers.
- focus groups with vets and farmers
- questionnaires to vets and farmers .

Knowledge Base
Responsibility
Vet-client Relationship
Agricultural Factors
Disease Epidemiology and Outcomes
Drug-related Factors
Economic Factors
External Pressures

Prophylactic use

'I do believe in prophylactic treatments because there are too many times where you try and not use antibiotics and then you end up with a bad mortality…'

'I think the one [prescribing practice] that we as pig veterinarians are weak on are the habitual repeat users. It's the repeated in feed prescription that's the issue, isn't it? I'm as guilty as the next man of that.'

Tylan is a growth promoter. It is used as a growth promoter. There are thousands and thousands of tons of Tylan going in at relatively low rates. Whether you say it's against lawsonia, or whatever you call it, or whether you say it's growth…'

I think the hardest thing in pig production at the moment is obviously… antibiotics are used as a management tool. But there aren't the financial rewards in pig production at the moment for people to actually go out and spend money on improving the use, improving the management to make that happen.'

Use in animals and resistance n humans

'human bacterial resistance, is from antibiotic use in humans, rather than transfer from animals' (v)

'…it's [antimicrobial resistance] obviously an issue in human medicine, which I think they're probably using us as the scape goats for. At the moment I think we've just got to be seen to conform or to reduce our usages to take the party line.' (v)

'My opinion, personally, is that if the doctors and the human health control was more under control, we would probably get less resistance.' (F)

Should we be saying we shouldn't be letting humans have antibiotic? In terms of why are we so hell bent on stopping animals when it's the humans themselves in some respects that are causing all their own problems?' (F)

'I think there's a greater danger when they're dished out like Smarties in GP practices for somebody with a common cold.'

Stewardship

- Good stewardship ***requires a multi-faceted approach.***
- '***One size fits All'-*** not likely to work
  - Different sectors, different countries, different production systems
- Education ?
  - Vets, farmers, owners, nurses, dispensers
- Regulation
  - Bans/restrictions on use?
  - Penalising non-compliance?
  - Targets for reduction?
  - May drive improper use

Acknowledgements

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All of the veterinary surgeons and farmers who gave their time .