



A structured approach to guideline development

OUR EXPERIENCE OF THE AGREE II FRAMEWORK

FERGUS ALLERTON

EBVS SPECIALIST IN SMALL ANIMAL INTERNAL MEDICINE

Workshop on developing national antimicrobial therapy
guidelines in Southeast Asia | 27 January 2022

Virtual 14:00—17:00 (BKK time)

Antibiotic Ω

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

Antimicrobial Resistance Collaborators*

www.thelancet.com Published online January 20, 2022 [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)

Since antibiotic use drives antibiotic resistance:

- need to ensure all use is appropriate.

In the UK:

25% dogs and 21% cats received ≥ 1 antibiotic over a 2 year period

6% prescriptions in dogs and 32% in cats - HPClAs





PROTECT ME

Prescribe only when necessary

- Consider non-bacterial disease (e.g. viral infection, nutritional imbalance, metabolic disorders)
- Remember that some bacterial diseases will self-resolve without antibacterials
- Offer a non-prescription form (see box bottom right)

Reduce prophylaxis

- Perioperative antibacterials are NOT a substitute for surgical asepsis
- Prophylactic antibacterials are only appropriate in some immunocompromised patients

Offer other options

- Consider therapeutic alternatives (lavage and debridement of infected material, cough suppressants, fluid therapy, nutritional modification)
- Using topical preparations reduces selection pressure on resident intestinal flora (the microbiome)
- Use effective hygiene techniques and antiseptics to prevent infections

Treat effectively

- Consider which bacteria are likely to be involved
- Consider drug penetration of the target site
- Use the shortest effective course and avoid underdosing
- Ensure compliance with appropriate formulation and provide clear instructions

Employ narrow spectrum

- Unnecessarily broad-spectrum antibacterials could promote antibacterial resistance
- The use of narrow-spectrum antibacterials limits effects on commensal bacteria
- Use culture results to support de-escalation (switching to a narrower spectrum antibacterial)

Culture appropriately

- A sample for culture should be collected **before** starting antibacterial therapy wherever possible
- Culture is essential when prolonged (>week) treatment courses are anticipated, when resistance is likely (e.g. hospital acquired infections) and in life-threatening infections
- If first-line treatment fails, do not use another antibacterial without supportive culture and sensitivity results (**avoid cycling antibacterials**)

Tailor your practice policy

- A customized practice policy can guide antibacterial selection to address the bacterial infections and resistance patterns that you encounter, minimizing inappropriate use
- Complete the tick boxes in this poster to highlight your practice's first-line approach to each condition

Monitor

- Track and record culture profiles and update your practice policy accordingly
- Monitor for preventable infections (e.g. postoperative) and alter practices if needed
- Audit your own antibacterial use, particularly of critically important antibacterials (fluoroquinolones/cefovecin, e.g. using mySasnet AMR)

Educate others

- Share this important message to reduce the threat from multi-resistant strains of bacteria and improve the health of pets and people

Antibacterial use in our practice

The antibiotic guardian(s) of this practice is/are:



Select which antibacterials your practice uses in the boxes below

Culture essential to ensure effective therapy

Culture strongly advised to guide therapy (where possible)

Use your smartphone and a QR code reader to access extra information. Alternatively visit: bsavalibrary.com/protectme

GASTROINTESTINAL INFECTIONS

Antibacterials are not indicated for:

- Acute vomiting
- Acute diarrhoea (including acute haemorrhagic cases)
- Pancreatitis
- Most gastric *Helicobacter* infections
- Most *Campylobacter*, *Salmonella*, *Clostridium perfringens* or *C. difficile* infections
- Chronic diarrhoea (except as part of a treatment trial)

Acute diarrhoea with systemic signs indicating actual (or risk of) bacteraemia or sepsis:

Suspected parvovirus
 Amoxicillin/clavulanate
 Amoxicillin/clavulanate
 Cefalexin
 Oxytetracycline

Trial treatment of chronic diarrhoea/chronic enteropathy (inflammatory bowel disease):

Metronidazole
 Tylosin
 Oxytetracycline

Prior to antibacterial trial, perform appropriate diagnostics and consider other treatments including Giardia treatment, dietary change or prednisolone trial. Trial antibacterial treatment should not exceed 3-4 weeks

Cholangitis/cholangiohepatitis:

- Amoxicillin/clavulanate
- Ampicillin
- Cefalexin
- Add metronidazole (dogs)

URINARY TRACT INFECTIONS

Antibacterials are not indicated for:

- Feline idiopathic cystitis (FIC)
- Feline struvite urolithiasis and canine non-struvite urolithiasis
- Urinary incontinence
- Subclinical bacteriuria (canine or feline)
- Juvenile canine vaginitis

Uncomplicated, symptomatic, canine urinary tract infection (cystitis):

- Amoxicillin (± clavulanate)
- Trimethoprim/sulphonamide

Reinfection, recurrent and persistent urinary tract infections:

- Amoxicillin (± clavulanate)
- Trimethoprim/sulphonamide

If reinfection occurs, use the SAME antibacterial if previously successful. If recurrent/persistent infection, modify therapy on basis of sensitivity data. Review predisposing factors (e.g. urolithiasis, anatomical abnormalities)

Prostatitis (entire males):

- Fluoroquinolones (high dose - see QR code)
- Trimethoprim/sulphonamide

Urolithiasis (± crystalluria):

- Canine struvite urolithiasis (for dissolution)
- Amoxicillin (± clavulanate) until resolution of urolithiasis confirmed
- Dietary modification and urine acidification alongside treatment
- Consider surgical removal

Suspected pyelonephritis:

- Amoxicillin/clavulanate
- Fluoroquinolones
- Trimethoprim/sulphonamide

EYE INFECTIONS

Canine conjunctivitis:

- Fusidic acid
- Chlorotetracycline

Severe gingivitis and periodontitis:

- Amoxicillin/clavulanate
- Metronidazole
- Clindamycin (if periodontal bone infection)

Feline conjunctivitis:

- Chlorotetracycline
- Fusidic acid

Feline-specific disease:

- Chlamydia felis*
- Systemic doxycycline (amoxicillin/clavulanate in pregnant queens and kittens)
- Malassezia dermatitis
- Treat for 21-28 days

Mycoplasma felis:

- Topical tetracycline

Uncomplicated corneal ulceration:

- Topical chloramphenicol

Complicated corneal ulceration/infectious keratitis:

- Topical chloramphenicol AND
- Topical gentamicin
- Topical ciprofloxacin
- Topical ofloxacin

Treat until the corneal defect has re-epithelialized q4 hours for the first 48 hours - reduced once the destructive corneal process has stopped. Consider systemic antibacterial if, e.g. 'melting', corneal perforation, marked uveitis

Orbital abscess/bacterial cellulitis:

- Amoxicillin/clavulanate
- Cefalexin and metronidazole
- Cefalexin and clindamycin

Acute bite wound prophylaxis:

- Thorough flushing with saline or 2-4% chlorhexidine
- Amoxicillin/clavulanate (for 7 days)

Surface pyoderma (hot spots, intertrigo):

- Topical treatment ONLY
- 2-4% chlorhexidine
- Fusidic acid ± glucocorticoid
- Silver sulphadiazine (if rods)

Superficial pyoderma:

- Topical treatment ONLY is appropriate
- 2-4% chlorhexidine

If required:

- Clindamycin
- Cefalexin
- Amoxicillin/clavulanate
- Trimethoprim/sulphonamide

Neutropenia:

- Mild (neutrophil count >1000/µl) - antibacterial NOT required
- Moderate (neutrophil count 500-999/µl) AND well
- Cefalexin
- Amoxicillin/clavulanate
- Trimethoprim/sulphonamide

Septic peritonitis secondary to gastrointestinal leakage:

- Metronidazole + marbofloxacin
- Ampicillin + amikacin + metronidazole
- Amoxicillin/clavulanate + marbofloxacin

Bacteraemia/sepsis (including peritonitis of non-gastrointestinal origin):

- Clindamycin + marbofloxacin
- Ampicillin + metronidazole + marbofloxacin
- Ampicillin + amikacin + marbofloxacin
- Amoxicillin/clavulanate + marbofloxacin

Orthopaedic infections:

- Discoepiphysitis:
- Cefalexin
- Amoxicillin/clavulanate
- Trimethoprim/sulphonamide
- Clindamycin

Prostatis (entire males):

- Fluoroquinolones (high dose - see QR code)
- Trimethoprim/sulphonamide

Inflective/septic arthritis:

- Cefalexin
- Amoxicillin/clavulanate

Osteomyelitis:

- Cefalexin
- Fluoroquinolones
- Trimethoprim/sulphonamide

ORAL INFECTIONS

Consider chlorhexidine mouthwash

Antibacterials are not indicated for:

- Malassezia dermatitis
- Non-specific skin problems (e.g. pruritus)

SKIN AND EAR INFECTIONS

Antibacterials are not indicated for:

- Malassezia dermatitis
- Non-specific skin problems (e.g. pruritus)

Bites and traumatic wounds:

- Debride and lavage
- If systemically well and not pyrexic:
- Topical treatment with 2-4% chlorhexidine
- If systemically unwell and pyrexic:
- Systemic antibacterials based on cytology.

For cocci:

- Clindamycin
- Cefalexin
- Amoxicillin/clavulanate
- Trimethoprim/sulphonamide

For rods:

- Fluoroquinolones

Acute bite wound prophylaxis:

- Thorough flushing with saline or 2-4% chlorhexidine
- Amoxicillin/clavulanate (for 7 days)

Surface pyoderma (hot spots, intertrigo):

- Topical treatment ONLY
- 2-4% chlorhexidine
- Fusidic acid ± glucocorticoid
- Silver sulphadiazine (if rods)

Superficial pyoderma:

- Topical treatment ONLY is appropriate
- 2-4% chlorhexidine

If required:

- Clindamycin
- Cefalexin
- Amoxicillin/clavulanate
- Trimethoprim/sulphonamide

Neutropenia:

- Mild (neutrophil count >1000/µl) - antibacterial NOT required
- Moderate (neutrophil count 500-999/µl) AND well
- Cefalexin
- Amoxicillin/clavulanate
- Trimethoprim/sulphonamide

Septic peritonitis secondary to gastrointestinal leakage:

- Metronidazole + marbofloxacin
- Ampicillin + amikacin + metronidazole
- Amoxicillin/clavulanate + marbofloxacin

Bacteraemia/sepsis (including peritonitis of non-gastrointestinal origin):

- Clindamycin + marbofloxacin
- Ampicillin + metronidazole + marbofloxacin
- Ampicillin + amikacin + marbofloxacin
- Amoxicillin/clavulanate + marbofloxacin

Orthopaedic infections:

- Discoepiphysitis:
- Cefalexin
- Amoxicillin/clavulanate
- Trimethoprim/sulphonamide
- Clindamycin

Prostatis (entire males):

- Fluoroquinolones (high dose - see QR code)
- Trimethoprim/sulphonamide

Inflective/septic arthritis:

- Cefalexin
- Amoxicillin/clavulanate

Osteomyelitis:

- Cefalexin
- Fluoroquinolones
- Trimethoprim/sulphonamide

RESPIRATORY INFECTIONS

Antibacterials are not indicated for:

- Chronic bronchitis/allergic airway disease unless secondarily infected
- Canine sino-nasal disease

Canine infectious respiratory disease complex (Kennel Cough) and Feline upper respiratory tract infection (Cat Flu):

- ONLY if clinical signs present >10 days and/or systemically unwell
- Doxycycline
- Amoxicillin/clavulanate

Pneumonia:

- Amoxicillin/clavulanate
- For suspected *Bordetella/Mycoplasma*
- Doxycycline

If antibacterial exposure in preceding 4 weeks or if hospitalized for >48 hours prior to onset of respiratory signs (i.e. hospital-acquired infection)

- Fluoroquinolone + clindamycin

Treat for 4-6 weeks, based on C-reactive protein, or for 7-10 days beyond radiographic resolution

Pyothorax:

- Fluoroquinolone + amoxicillin (± clavulanate)
- Fluoroquinolone + clindamycin

Treat for 4-6 weeks (and beyond radiographic/ultrasonographic resolution)

SURGICAL USE

Antibacterials are not indicated for:

- Clean (elective surgery, no entry into hollow viscus) surgical procedures

Prophylactic (perioperative) antibacterials are appropriate:

- For prolonged clean surgery (>90 minutes) or surgery involving an implant
- Where there is an obvious break in asepsis causing contamination of the wound
- For all contaminated wounds or if there is a pre-existing infection
- For debilitated or immunosuppressed patients
- Where infections would be catastrophic (e.g. in CNS)

In most cases:

- Amoxicillin/clavulanate
- Cefuroxime
- Cefazolin

Intravenously 60 minutes before the first incision, then every 90 minutes until the end of surgery

- Where anaerobic involvement is highly likely:
- Add metronidazole

Do not continue antibacterials after surgery, unless there is a therapeutic indication as this will select for resistance

Therapeutic (postoperative) antibacterials are indicated:

- To treat a known bacterial infection
- When the risk of a postoperative infection developing is high due to contamination or major break in asepsis

MISCELLANEOUS INFECTIONS

Pyometra:

- Antibacterials not required if stable and proceeding directly to OHE
- Surgically managed:
- Amoxicillin (± clavulanate)
- Cefalexin + enrofloxacin

Treatment discontinued after surgery (unless septic peritonitis)

Medically managed:

- Amoxicillin (± clavulanate)

Mastitis:

- Cefalexin
- Amoxicillin/clavulanate
- Trimethoprim/sulphonamide

Treat for 2-3 weeks or until offspring weaned (early weaning NOT advised)

Suspected *Mycoplasma haemofelis* (feline infectious anaemia):

- Doxycycline
- Marbofloxacin

Treat for 4 weeks

Suspected leptospirosis:

- Doxycycline
- Penicillin G
- Amoxicillin (± clavulanate)

Doxycycline is necessary to address renal colonization/carrier state

- Treat for 2 weeks

Hepatic encephalopathy (HE):

- Diet and lactulose should be first line therapies in the management of patients with HE
- If symptomatic:
- Metronidazole (decreased dose)
- Amoxicillin
- Ampicillin

ADVERSE REACTIONS TO ANTIBACTERIALS

This list is not comprehensive.

Antimicrobial	Adverse effect	At risk group	Recommendation
Aminoglycosides	Nephrotoxicity	Dogs/cats with pre-existing renal disease, volume or electrolyte depletion	Avoid in at risk animals or when close monitoring is not available. Do not exceed 7 days treatment duration. Monitor urine for casts
Amoxicillin/clavulanate (intravenous use)	Urticaria, hypotension. Anaphylactoid reactions	Cats	Caution with intravenous use in anaesthetized patients
Doxycycline or clindamycin	Oesophageal irritation ± stricture	Dogs (>dogs)	Ensure administration with food or water
Enrofloxacin	Retinal degeneration leading to partial, temporary or total blindness	Cats	Alternative fluoroquinolones preferred in cats
Fluoroquinolones	Defective cartilage development leading to severe lameness	Young dogs	Avoid in growing animals
Metronidazole	Dose-dependent neurotoxicity	Dogs	Caution with higher doses
Penicillins	Immediate and delayed hypersensitivity reactions	Dogs/cats	Avoid in penicillin-sensitive animals/owners
Potentiated sulphonamides	Keratoconjunctivitis sicca. Hepatic necrosis (rare). Immune complex reactions (polyarthritis, anemias, thrombocytopenia)	Dogs esp. Dobermanns, Samoyeds and Miniature Schnauzers	Avoid in specified breeds. Monitor Schirmer Tear Test before and during use

DO NOT USE

Antibacterials with restricted use in human medicine (e.g. imipenem, linezolid, teicoplanin, vancomycin) should **not** be used in animals.

Highest priority critically important antibacterials

Fluoroquinolones (enrofloxacin, marbofloxacin, pradofloxacin, ciprofloxacin), and 3rd- and 4th-generation cephalosporins (cefovecin) should **only** be used when first-line antibacterials are inappropriate or ineffective. If urgent treatment is required, then samples for culture and sensitivity testing should be submitted before starting these agents, and then therapy adapted.

First-line antibacterials

Limit the use of first-line antibacterials to times of genuine clinical need and avoid all unnecessary use.

Responsible antibacterial use under the Cascade

It is justifiable, on a case-by-case basis, to prescribe an antibiotic on the cascade in the interests of minimizing the development of resistance, particularly where culture and sensitivity data indicate that a particular antibiotic active substance is effective against a bacterial pathogen and where knowledge of pharmacokinetics indicates that the selected product is likely to be safe and effective for the animal species and condition being treated.



Other guidelines are available...

Country	Last Updated	Antimicrobial Stewardship Guidelines (ASGs)
Belgium	2020 [29]	Formularium Antimicrobial Consumption and Resistance in Animals (AMCRA)
Denmark	2018 [30]	Antibiotic Use Guidelines for Companion Animal Practice (2nd Edition) *
Finland	2018 [31]	Mikrobilääkkeiden käyttösuositukset eläinten tärkeimpiin tulehdus- ja tartuntatauteihin *
France	2017 [32]	Guide De Bonnes Pratiques Filière Animaux De Compagnie Fiches De Recommandations Pour Un Bon Usage Des Antibiotiques 2017
Italy	2017 [33]	Linee guida. Uso prudente dell'antibiotico negli animali da compagnia
	2017 [34]	Linee Guida sul corretto uso degli antibiotici nella clinica del cane e del gatto
Netherlands	2017 [35]	Formularium gezelschapsdieren hond, kat en konijn
Norway	2014 [36]	Terapianbefaling: Bruk av antibakterielle midler til hund og katt
Sweden	2010 [37]	Guidelines for the clinical use of antibiotics in the treatment of dogs and cats *
Switzerland	2019 [38]	Therapieleitfaden für Tierärztinnen und Tierärzte—Hunde und Katzen
	2020 [39]	AntibioticScout.ch
Turkey	2017 [40]	Veteriner Hekimlikte Antibiyotikler (Pratik Bilgiler Rehberi) 2nd Edition
United Kingdom	2018 [41]	PROTECT ME poster *
FECAVA	2018 [42]	FECAVA Recommendations for Appropriate Antimicrobial Therapy *
GRAM book	2016 [43]	Guidance for the rational use of antimicrobials *

Those marked with an asterisk (*) are also available in English.

A consistent message

Table 2. Frequency of recommendations in ASGs.

Recommendation	Number of ASGs (n = 15)	Percentage of ASGs (%)
Antimicrobials are not indicated for management of:		
Acute diarrhea	15	100
Clean/elective surgical procedures	13	87
Feline lower urinary tract disease	11	73
subclinical bacteriuria	8	53
Non-antimicrobial therapeutic options described	14	93
Use topical medication instead of systemic medication where appropriate	15	100
Select narrow over broad-spectrum antimicrobials or encourage de-escalation to a narrower spectrum	13	87
Avoid certain antimicrobials reserved for human use only, e.g., vancomycin or carbapenems	12	80
Mention highest priority critically important antimicrobials (HPCIAAs)	10	66
Tier antimicrobial suggestions (first line, second line)	13	87
Promote use of diagnostic techniques (cytology/culture) to identify putative bacteria	15	100
List common pathogens found in specific conditions	14	93
Monitor local antimicrobial resistance patterns	5	33
Audit/monitor individual/practice AMU	8	53

Do guidelines work?

Antibiotika
Scout



Antimicrobial prescriptions in cats in Switzerland before and after the introduction of an online antimicrobial stewardship tool



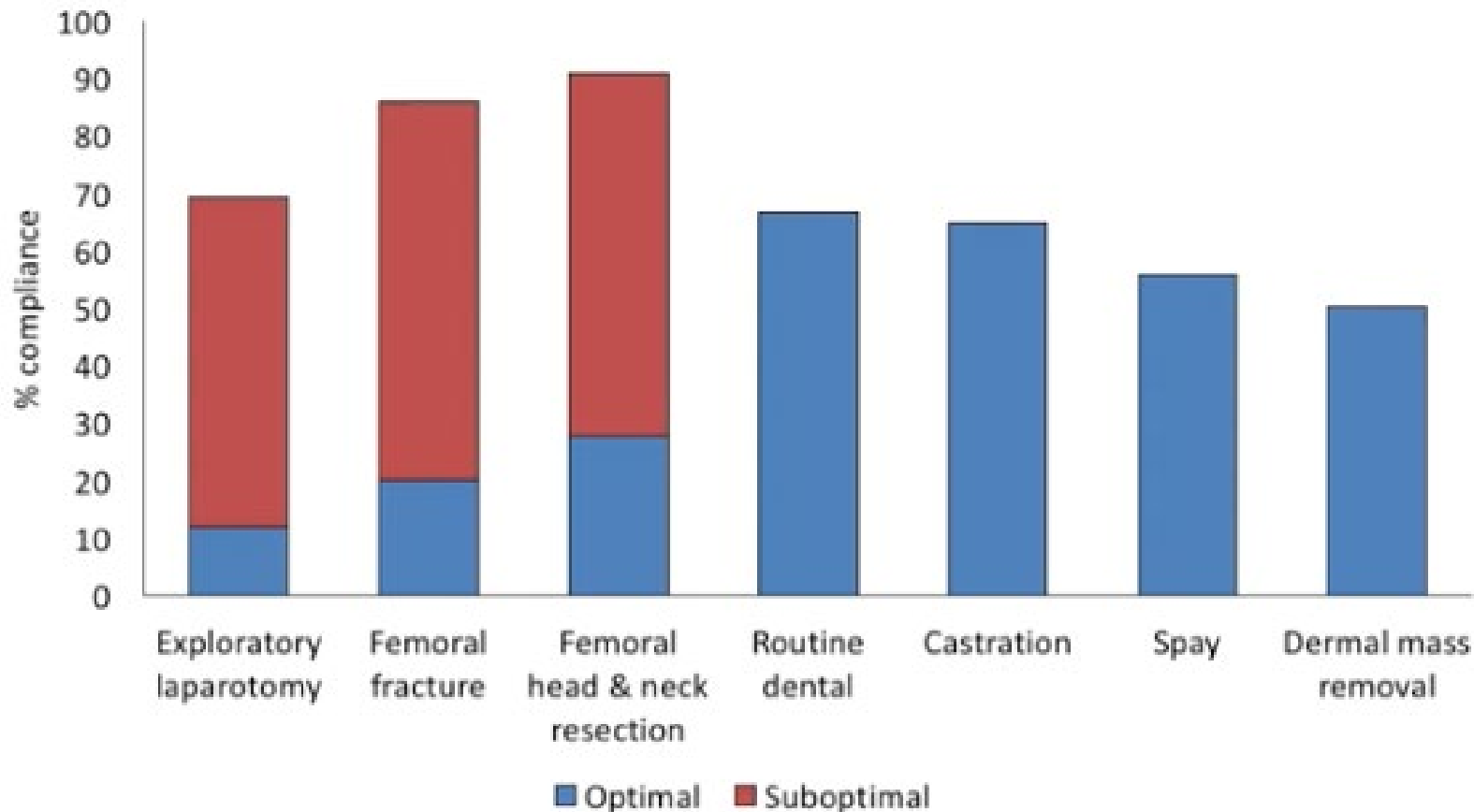
Hubbich *et al.* *BMC Veterinary Research* (2020) 16:229
<https://doi.org/10.1186/s12917-020-02447-8>

Conclusions: Overall proportions of antimicrobial prescription, unjustified antimicrobial therapy and, in private practices, use of 3rd generation cephalosporins decreased from 2016 to 2018 for the investigated feline diseases. However, overall compliance with Swiss prudent use guidelines was still low, implying that further efforts are required to foster prudent antimicrobial use in cats.

Compliance with guidelines

Antimicrobials used for surgical prophylaxis by companion animal veterinarians in Australia

Laura Y. Hardefeldt^{a,*}, Glenn F. Browning^a, Karin Thursky^b, James R. Gilkerson^a, Helen Billman-Jacobe^a, Mark A. Stevenson^a, Kirsten E. Bailey^a



WHY?

Guidelines can be ignored

Defensive medicine (just in case)

Diagnostic uncertainty

Pressure from owners (farmers?)

Need high-quality guidelines that will BE USED by stakeholders

Smith et al. *Antimicrobial Resistance and Infection Control* (2018) 7:46
<https://doi.org/10.1186/s13756-018-0341-1>

Antimicrobial Resistance
and Infection Control

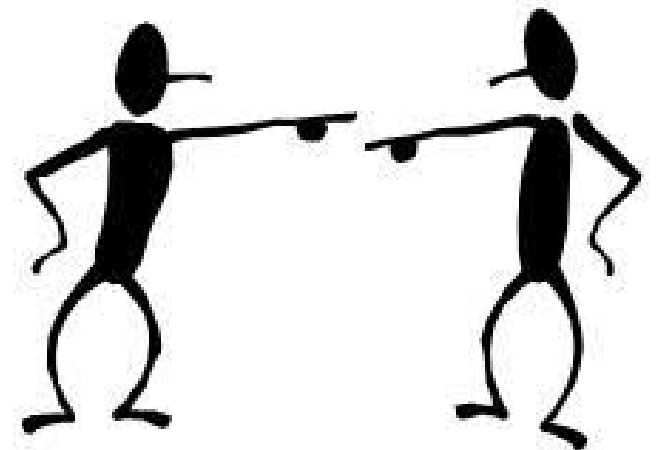
RESEARCH

Open Access

Pet owner and vet interactions: exploring the drivers of AMR



Matt Smith^{1*}, Caroline King¹, Mark Davis², Adele Dickson¹, Jeni Park¹, Fraser Smith¹, Kay Currie¹ and Paul Flowers¹



Agree II

The purpose of the AGREE II, is to provide a framework to:

1. Assess the quality of guidelines;
2. Provide a methodological strategy for the development of guidelines; and
3. Inform **what** information and **how** the information ought to be reported in guidelines.



Domains

Domain 1. Scope and Purpose is concerned with the overall aim of the guideline, the specific health questions, and the target population (items 1-3).

Domain 2. Stakeholder Involvement focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users (items 4-6).

Domain 3. Rigour of Development relates to the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them (items 7-14).

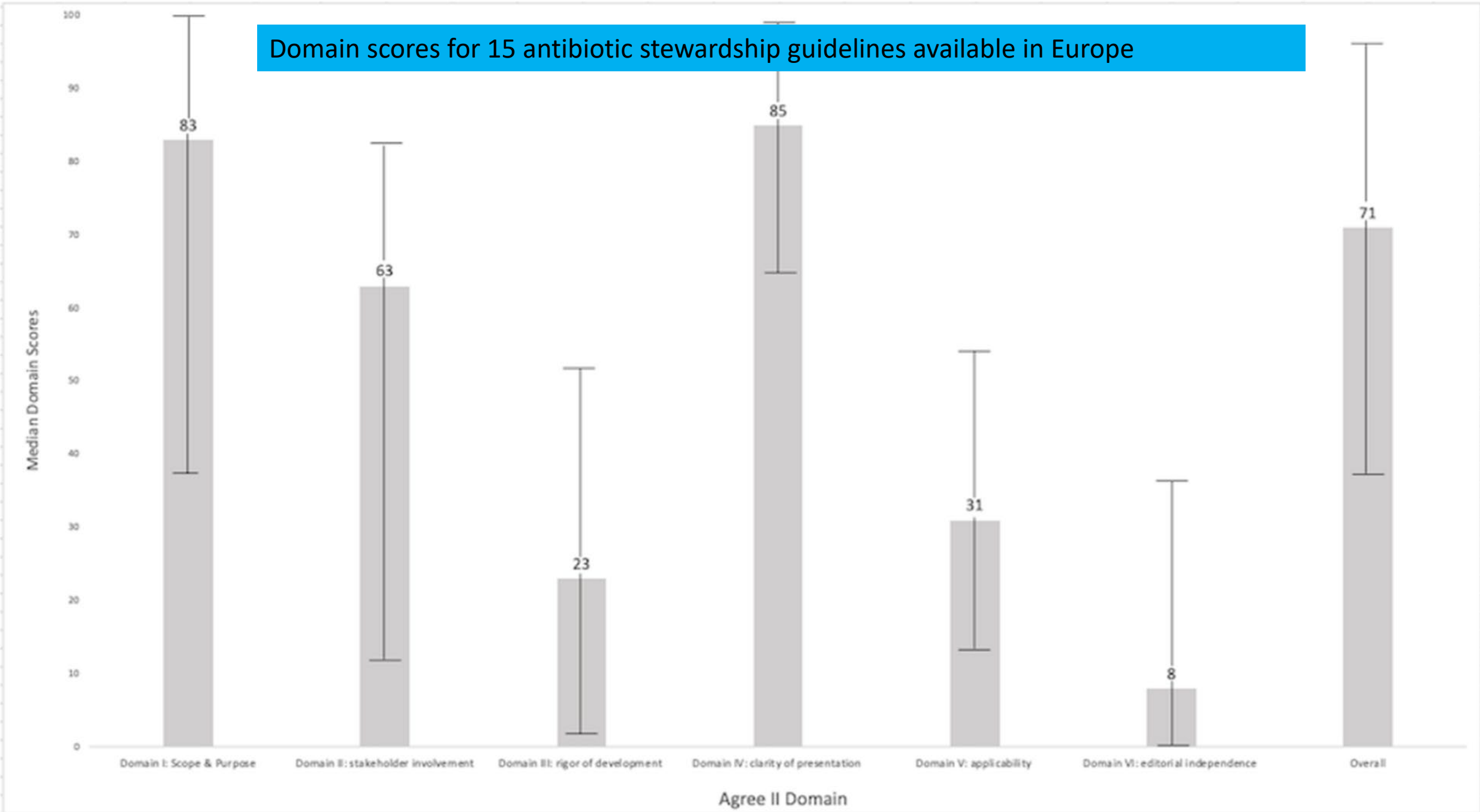
Domain 4. Clarity of Presentation deals with the language, structure, and format of the guideline (items 15-17).

Domain 5. Applicability pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline (items 18-21).

Domain 6. Editorial Independence is concerned with the formulation of recommendations not being unduly biased with competing interests (items 22-23).

Overall assessment includes the rating of the overall quality of the guideline and whether the guideline would be recommended for use in practice.

Domain scores for 15 antibiotic stewardship guidelines available in Europe

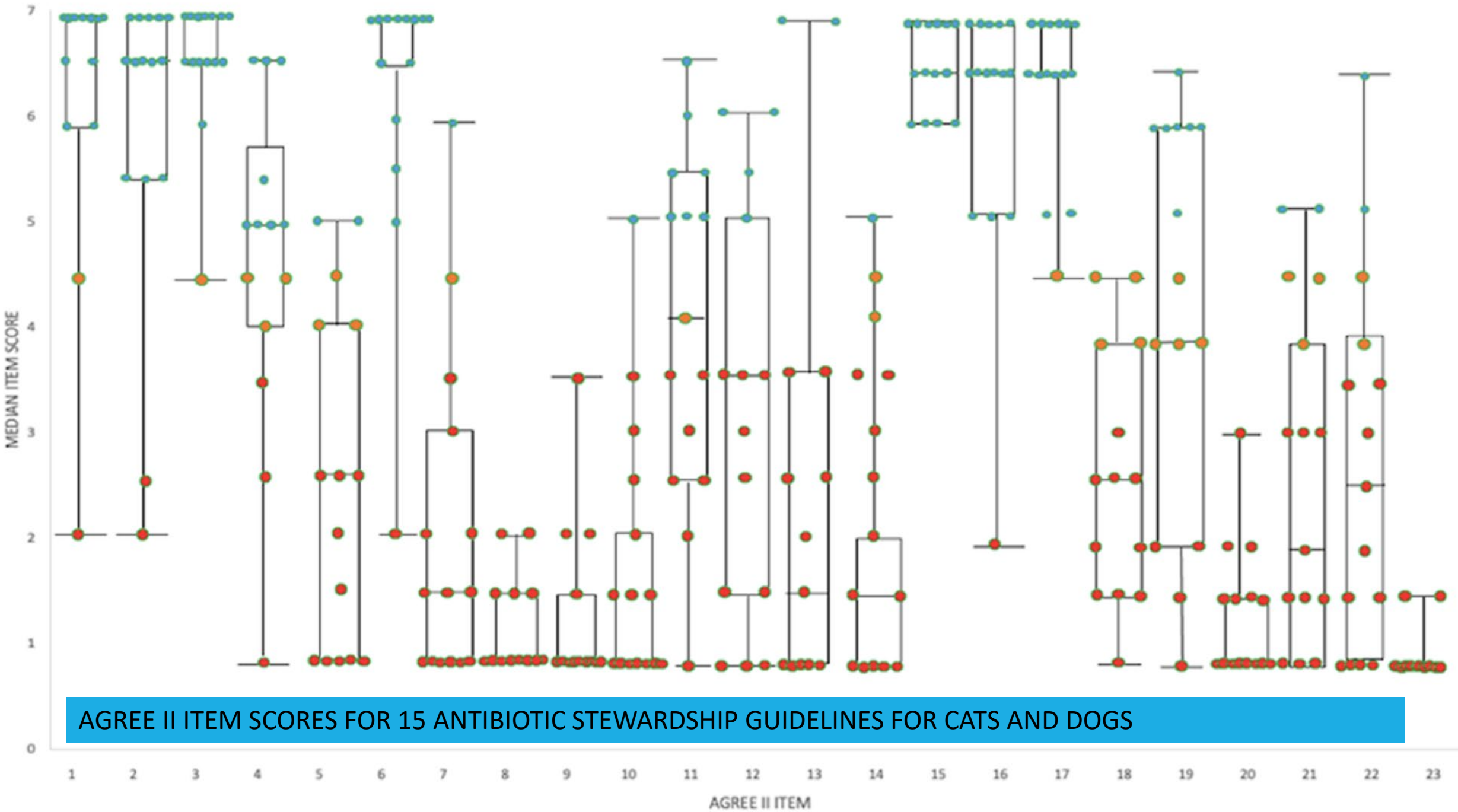


The Agree II tool

AGREE II Item	
1	The overall objective(s) of the guideline is (are) specifically described
2	The clinical question(s) covered by the guideline is (are) specifically described
3	The patients to whom the guideline is meant to apply are specifically described
4	The guideline development group includes individuals from all the relevant professional groups
5	The patients' views and preferences have been sought
6	The target users of the guideline are clearly defined
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	The health benefits, side effects, and risks have been considered in formulating the recommendations
12	There is an explicit link between the recommendations and the supporting evidence
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided
15	The recommendations are specific and unambiguous
16	The different options for management of the condition are clearly presented
17	Key recommendations are easily identifiable
18	The guideline is supported with tools for application
19	The potential organizational barriers in applying the recommendations have been discussed
20	The potential cost implications of applying the recommendations have been considered
21	The guideline presents key review criteria for monitoring and/ or audit purposes
22	The guideline is editorially independent from the funding body
23	Conflicts of interest of guideline development members have been recorded

Freely available:

<https://www.agreetrust.org/agree-ii/>



AGREE II ITEM SCORES FOR 15 ANTIBIOTIC STEWARDSHIP GUIDELINES FOR CATS AND DOGS

Conclusions

There are several excellent (and accessible) guidelines currently available

Important to understand needs of target stakeholders

Recommendations need regular updating to reflect new evidence

EBVM remains an optimistic objective

Agree II offers a logical framework to support this process



ENOVAT

**European Network for Optimization of
Veterinary Antimicrobial Treatment**



Thank you

fergus.allerton@willows.uk.net

Stop Antibiotic Resistance