Bridging the gap of innovation – what we all could do ?
Improving usage by guidelines: a critical view

Paul M. Tulkens

Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Université catholique de Louvain, Brussels, Belgium

http://www.facm.ucl.ac.be

21st ECCMID ICC

21st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) &
27th International Congress of Chemotherapy (ICC)
Milan, Italy, 7-10 May 2011

Disclosures

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- Other relationships in relation to this talk
  - Belgian Antibiotic Policy Coordination Committee, Belgian Transparency and Reimbursement Committees

What this lecture will be about ?

- Guidelines why ?
- Are guidelines unanimous on defined topics ?
- What is the quality of guidelines
- What could be their limitations in daily clinical practice ?
- Guidelines and drug innovation

the case of the CAP guidelines

a few words about vancomycin

Guidelines: origin, basis and use

- Clinical guideline aim at **guiding decisions and criteria** regarding diagnosis, management, and treatment
- Guidelines have been used since the beginning of Medicine
- Modern medical guidelines are supposed to be based on **critical examination of current evidence**, with emphasis on **evidence-based** rather than eminence-based medicine.
- More and more, healthcare professionals must not only know but apply guidelines or justify why they do not follow them for an individual patient or a group of patients.

Guidelines: content and goals

- Modern clinical should identify the **most valuable evidence** and integrate this knowledge to build **optimized decisions trees** that should be applicable to the majority of patients while being sufficiently flexible to accommodate a sufficient level of individual variation

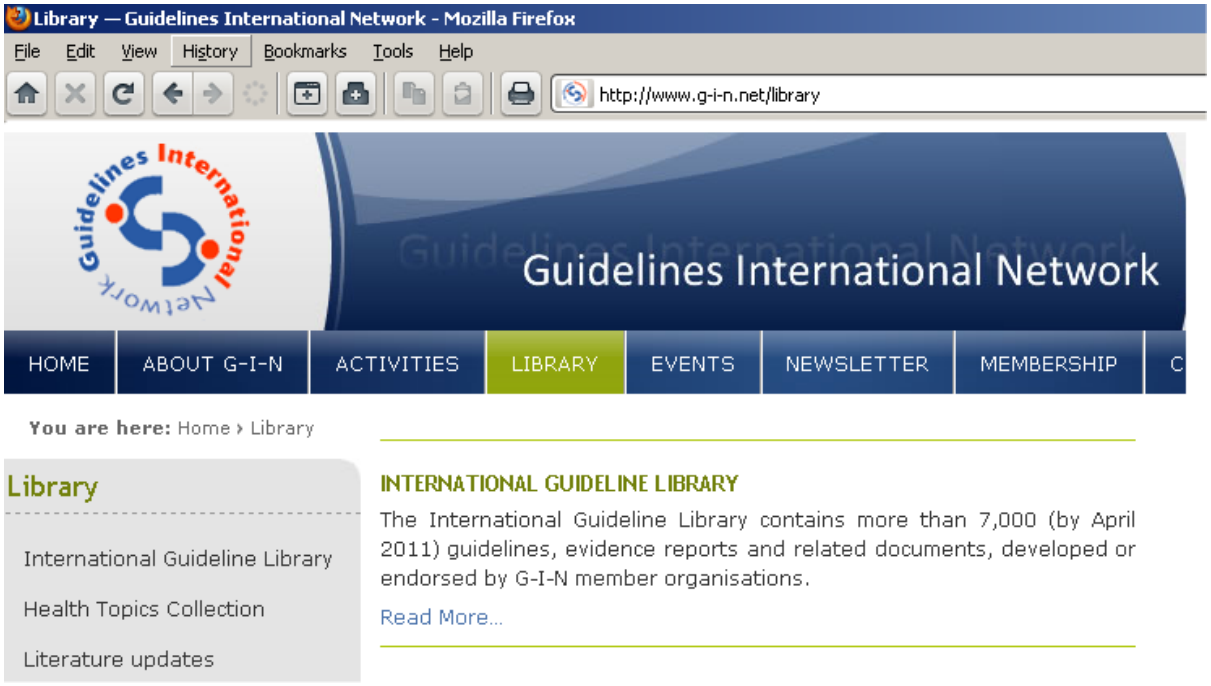
- But guidelines are also often seen as a mean to **standardize medical care** with 2 potential consequences/goals, namely

  - to **raise quality of care** while *reducing the risks* to patients

  - to achieve the **best balance between cost and medical efficacy** (broadly speaking)

Guidelines: who and where ?

- Guidelines at national or international levels by experts and associations that should represent not only the health care professionals but also the patients (individual level) and the society (societal level) and published in a variety of forms…
- Guidelines International Network (G-I-N) possesses the the largest web based data base of medical guidelines worldwide



Guidelines: are they used ?

- However, we know that even simple clinical practice guidelines are not as followed as they could be, which raise questions about their utility…

Example 1

BMC Family Practice

BioMed Central

Research article

Open Access

The attitude of Belgian social insurance physicians towards evidence-based practice and clinical practice guidelines

Annemie Heselmans*[1], Peter Donceel[†1], Bert Aertgeerts[†1,2], Stijn Van de Velde[†1,2] and Dirk Ramaekers[†1,2,3]

BMC Family Practice 2009, **10**:64

Conclusion: Although the majority of physicians were positive towards EBM and welcomed more guidelines, the use of evidence and clinical practice guidelines in insurance medicine is low at present. It is in the first place important to eradicate the perceived inertia which limits the use of EBM and to further investigate the EBM principles in the context of insurance medicine. Available high-quality evidence-based resources (at the moment mainly originating from other medical fields) need to be structured in a way that is useful for insurance physicians and global access to this information needs to be ensured.

Guidelines: are they used ?

Example 2

Journal of Antimicrobial Chemotherapy (2008) **62**, 189–195
doi:10.1093/jac/dkn143
Advance Access publication 8 April 2008

JAC

Opposing expectations and suboptimal use of a local antibiotic hospital guideline: a qualitative study

Pieter-Jan Cortoos[1]*, Karel De Witte[2], Willy E. Peetermans[3], Steven Simoens[1] and Gert Laekeman[1]

[1]Research Centre for Pharmaceutical Care and Pharmaco-economics, Katholieke Universiteit Leuven, O&N 2, Herestraat 49, PB 521, B-3000 Leuven, Belgium; [2]Centre for Organisation and Personnel Psychology, Katholieke Universiteit Leuven, Tiensestraat 102, PB 3725, B-3000 Leuven, Belgium; [3]University Hospitals of Leuven, Department of General Internal Medicine and Infectious Diseases, Herestraat 49, PB 7003, B-3000 Leuven, Belgium

Conclusions: **Locally developed hospital guidelines experience the same barriers as other guidelines. Within one hospital, prescribers have to be seen as a number of different target groups instead of a homogeneous population. For an optimal effect, interventions will have to consider these differences. Also, in order to improve local guideline use and antibiotic consumption, supervisors have to be aware of how their role as opinion leaders can influence residents. Lastly, active guideline distribution and promotion remains critical to ensure efficient guideline use. Future research should focus on how to adapt interventions to these different target groups.**

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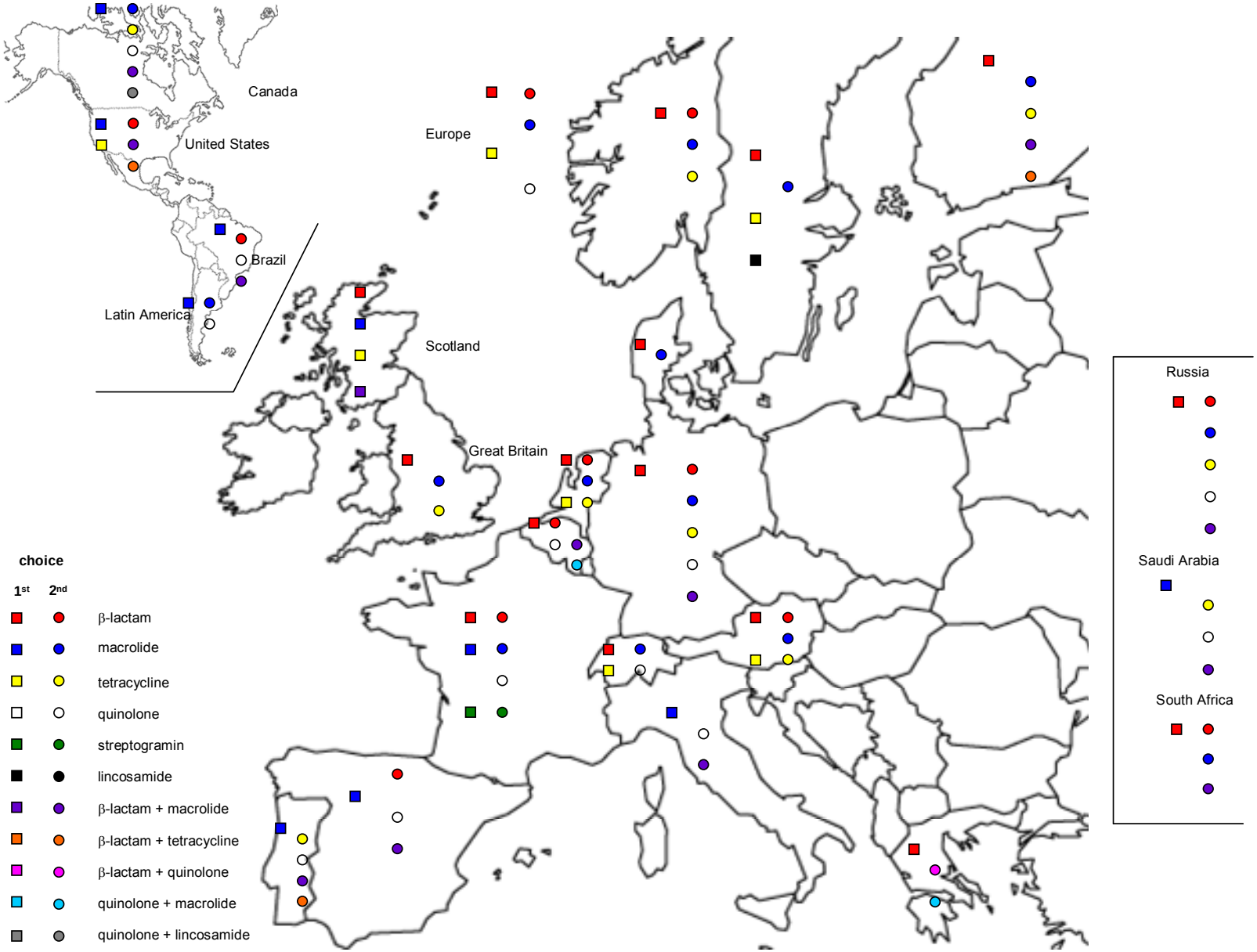
Guidelines: are they homogenous ?

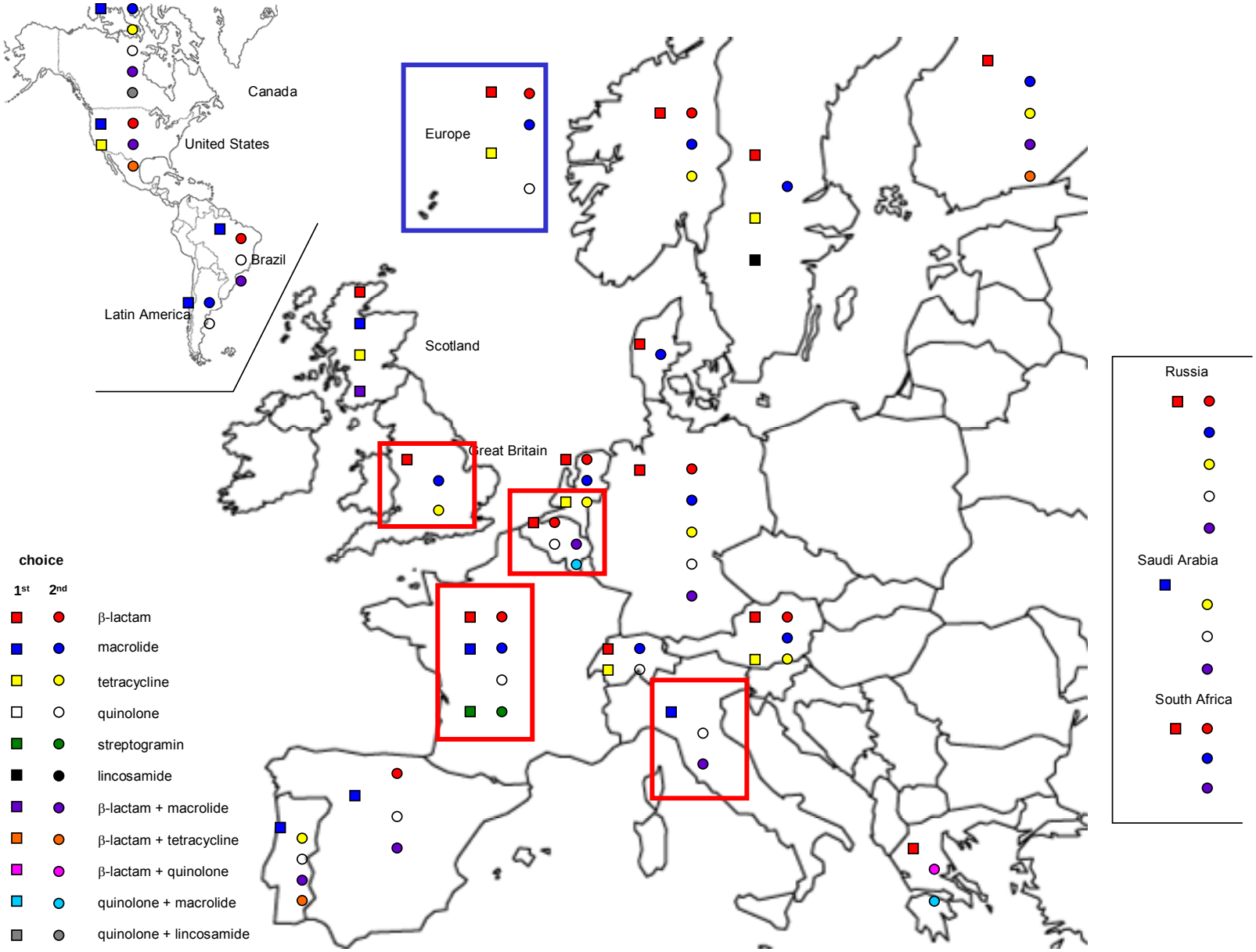
- They need not if
  - the diseases are different between geographical areas or groups of patients
  - for infectious diseases, if the epidemiology is different between areas
  - if drug availability is not uniform…
  - if medical and pharmaceutical resources are different

- However, variations are often much larger that what may be anticipated from the above considerations…

Guidelines: an example with CAP



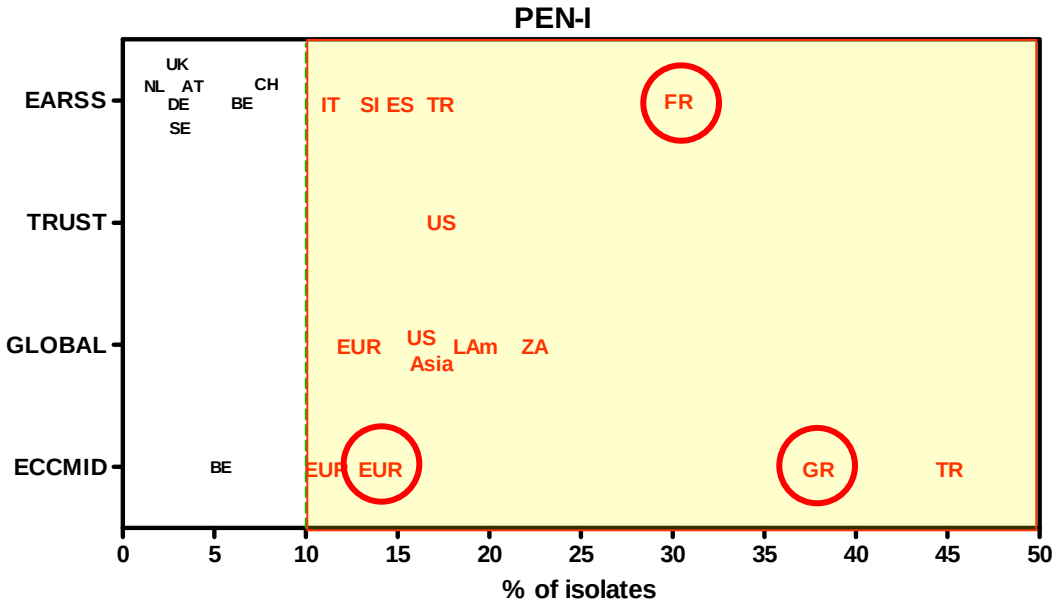
Guidelines: an example with CAP

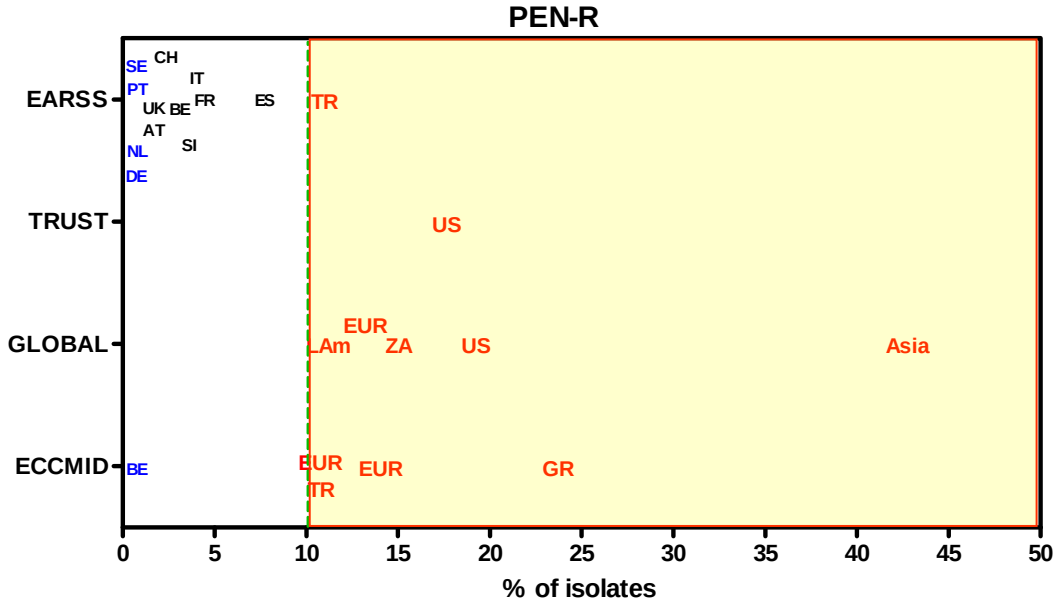


Populations at risk of bacteriological failure *

*analysis of resistance of 1st line antibiotics (penicillins) for CAP as reported by the surveillance systems or publications (*S. pneumoniae*)

- **EARSS**: European Antimicrobial Surveillance system
- **TRUST**: Tracking Resistance in the United States Today
- **GLOBAL**: Global Landscape On the Bactericidal Activity of Levofloxacin
- **ECCMID**: abstracts of the 18-20th European Congress of Clinical Microbiology and Infectious Diseases





Carbonnelle *et al.*, in preparation

Populations at risk of bacteriological failure *

*analysis of resistance of often recommended 1st line antibiotics for CAP (macrolides, doxycycline) as reported by surveillance systems or publications (*S. pneumoniae*)

- **EARSS**: European Antimicrobial Surveillance system
- **PROTEKT**: Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin
- **TRUST**: Tracking Resistance in the United States Today
- **GLOBAL**: Global Landscape On the Bactericidal Activity of Levofloxacin
- **Riedel:** Eur J Clin Microbiol Infect Dis. 2007 Jul;26(7):485-90.
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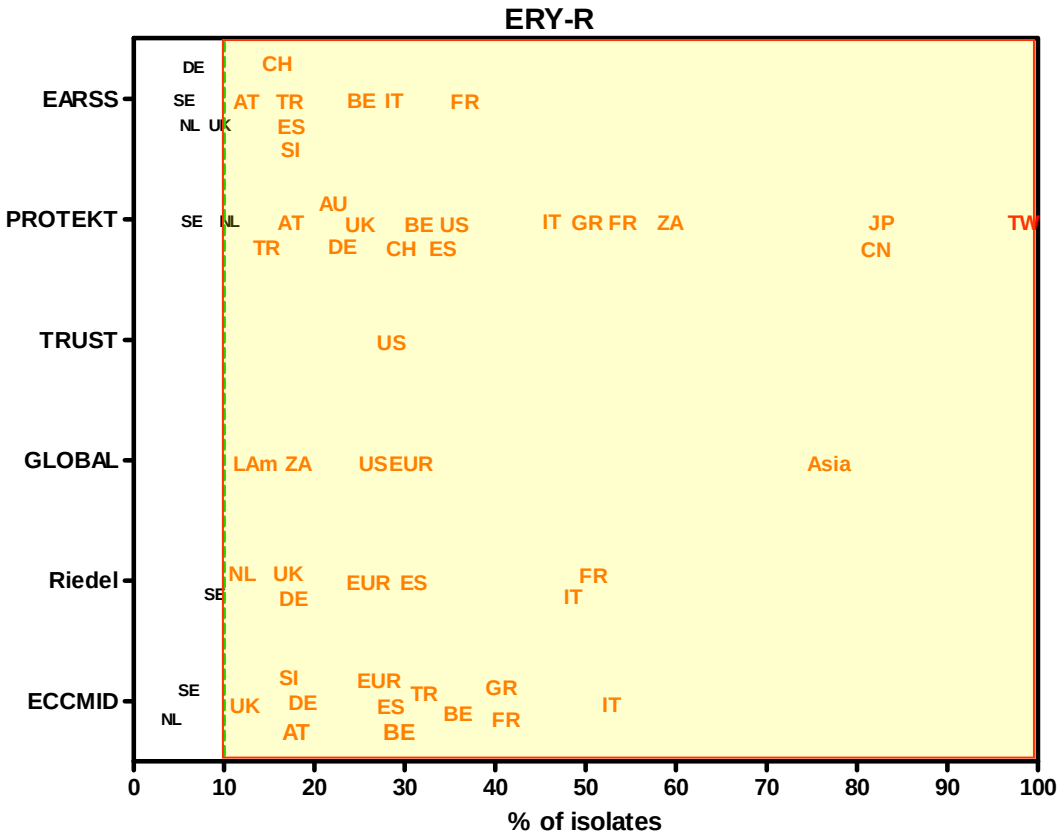
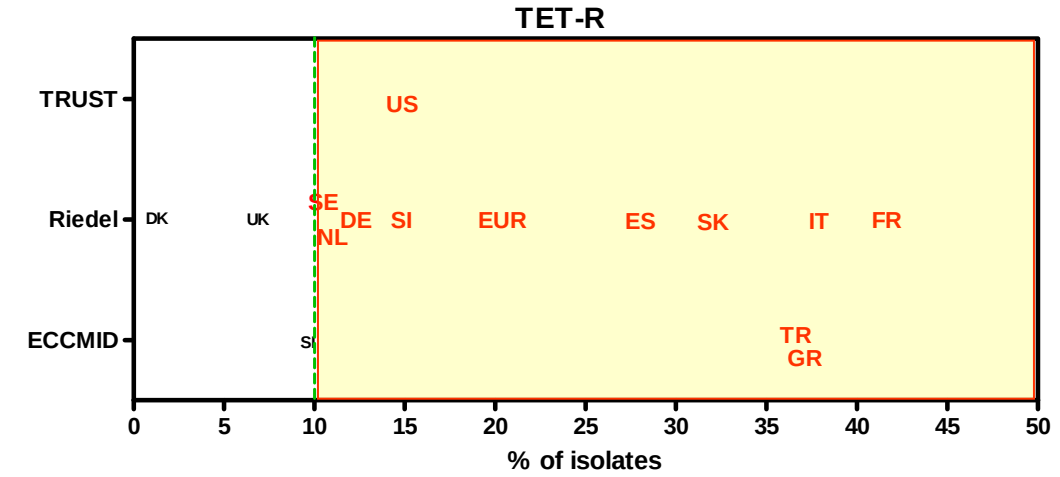
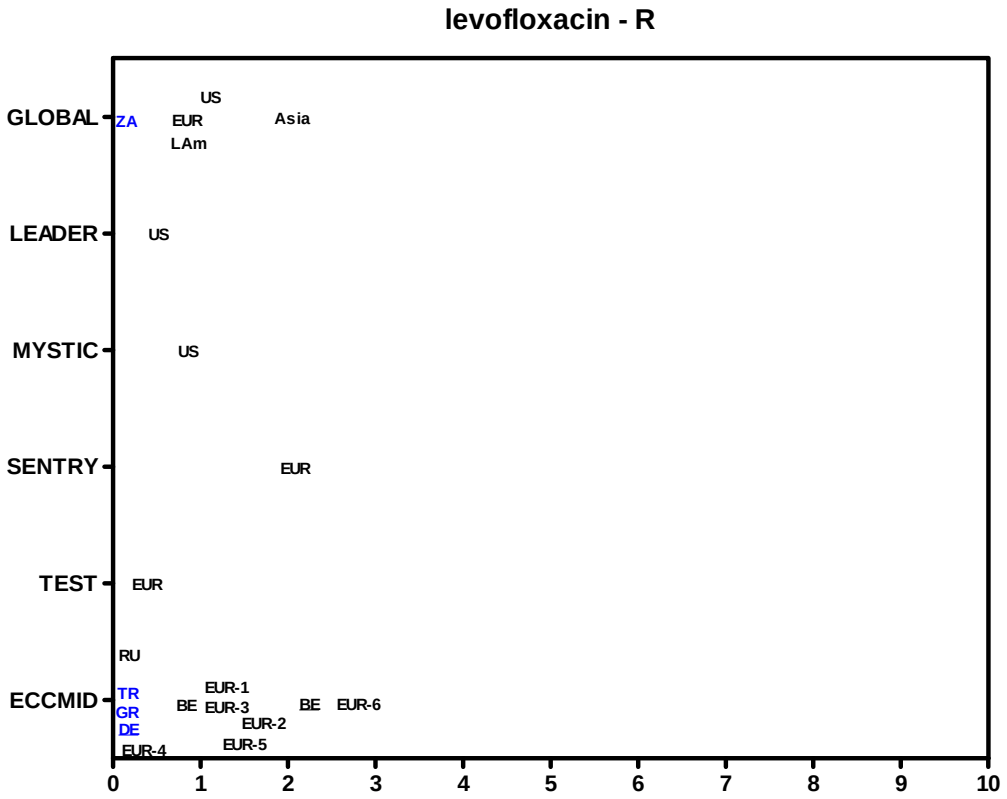




Populations at risk of bacteriological failure *

*analysis of resistance of fluoroquinolones (levofloxacin) as reported by surveillance systems or publications (*S. pneumoniae*)

- **GLOBAL**: Global Landscape On the Bactericidal Activity of Levofloxacin
- LEADER [Linezolid Surveillance Program
- SENTRY [Antimicrobial Surveillance Program]
- MYSTIC [Meropenem Yearly Susceptibility Test Information Collection]
- TEST [Tigecyline Evaluation Surveillance Trial
- **ECCMID**: abstracts of the 18-20th European Congress of Clinical Microbiology and Infectious Diseases



Carbonnelle *et al.*, in preparation

Are CAP guidelines based on the risk of emergence of resistance: the case of fluoroquinolones…

Journal of Antimicrobial Chemotherapy (2007) **60**, 965–972
doi:10.1093/jac/dkm292
Advance Access publication 10 August 2007

JAC

Selection of quinolone resistance in *Streptococcus pneumoniae* exposed *in vitro* to subinhibitory drug concentrations

Laetitia Avrain[1], Mark Garvey[2], Narcisa Mesaros[1], Youri Glupczynski[3], Marie-Paule Mingeot-Leclercq[1], Laura J. V. Piddock[2], Paul M. Tulkens[1], Raymond Vanhoof[4] and Françoise Van Bambeke[1]*

[1]*Université Catholique de Louvain, Unité de Pharmacologie Cellulaire et Moléculaire, Brussels, Belgium;* [2]*University of Birmingham, Division of Immunity and Infection, Birmingham, UK;* [3]*Université Catholique de Louvain, Cliniques Universitaires de Mont-Godinne, Laboratoire de Microbiologie, Yvoir, Belgium;* [4]*Pasteur Instituut, Antibiotica Resistentie en Nosocomiale Infecties, Brussels, Belgium*

J Antimicrob Chemother 2010; **65**: 2076–2082
doi:10.1093/jac/dkq287 Advance Access publication 13 August 2010

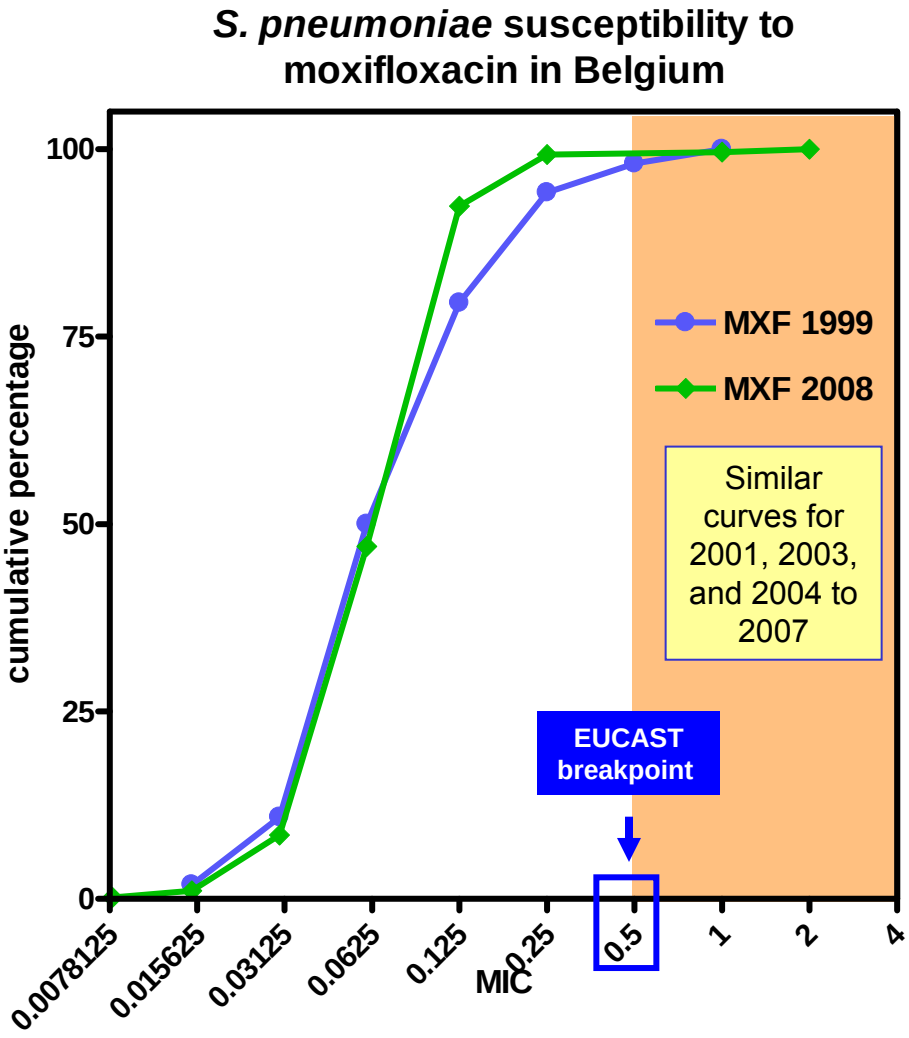
Journal of Antimicrobial Chemotherapy

Fluoroquinolones induce the expression of *patA* and *patB*, which encode ABC efflux pumps in *Streptococcus pneumoniae*

Farid El Garch[1]†, Ann Lismond[1], Laura J. V. Piddock[2], Patrice Courvalin[3], Paul M. Tulkens[1] and Françoise Van Bambeke[1]*

[1]*Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium;* [2]*School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK;* [3]*Institut Pasteur, Unité des Agents antibactériens, Paris, France*

Moxifloxacin MIC's against *S. pneumoniae* in Belgium from 1999 to 2008



From data of a <u>national</u> collection

- Non invasive respiratory tract infections
- similar results in 2008 for a collection of S.penumoniae from clinically-confirmed CAP)

Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates
(n=156 in 1999 and 448 in 2008)
http://www.iph. fgov.be
Data available yearly for 1999 through 2008.
Presented at 19th ECCMID, May 2009, Helsinki, Finland (Vanhoof et al.)

Populations at risk of side effects

Class	Drugs	Populations at higher risk of side effects
β-lactams	amoxicillin	• Allergic patients
	amoxicillin/ clavulanic acid	• Allergic patients • Erythematous skin rash: patients with mononucleosis • Hepatic toxicity: patients with hepatic dysfunction • Nephrotoxicity: elderly patients
macrolides	clarithromycin	• Cardiac effects: patients taking other drugs with effects on QTc or class 1A or III antiarrythmics • Pregnancy • Patients with severe renal impairment with or without coexisting hepatic impairment • Patients taking drugs metabolized by CYP450
	azithromycin	• Hepatotoxicity: patients with liver failure
	telithromycin	• Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia • Myopathies : co-administration of statins • Patients with severe renal impairment • Pregnancy • Children (no studies so far)

* as defined by the corresponding labelling

Carbonnelle *et al.*, in preparation

Populations at risk of side effects

Class	Drugs	Populations at higher risk of side effects
fluoroquinolones	levofloxacin	• Tendon disorders: elderly, patients taking corticoids, or with kidney, heart or lung transplants • Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia • CNS effects: patients at risk of epilepsy • Dysglycemia: diabetic patients • Pregnancy, lactation, infants
	moxifloxacin	• Tendon disorders: elderly, patients taking corticoids, or with kidney, heart or lung transplants • Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia • CNS effects: patients at risk of epilepsy • Pregnancy, lactation, infants
tetracyclines	doxycycline	• Pregnancy, lactation, infants

* as defined by the corresponding labelling

Carbonnelle *et al.*, in preparation

A survey of hepatotoxicity risk for antibiotics used in primary care (including CAP)

Ciprofloxacin Levofloxacin Moxifloxacin	Tetracycline	Erythromycin Clarithromycin Penicillins	Co-trimoxazole Amoxicillin/ clavulanate	Telithromycin
Isolated cases and ≤ 0.00007	≤0.0002	≤0.004	≤0.02	**Acute liver failure high mortality** ? Withdrawal or severe restriction does not allow calculating true incidences

Hepatotoxicity risk of antibiotics: percentage of prescriptions for antibiotics with main indications for use in the community setting.

(From Andrade & Tulkens, JAC 2011 – In press)

Why so much (apparent or real ?) problems ?

Several instruments have been devised to assess the quality of guidelines…

Editorial

Clinical practice guidelines: towards better quality guidelines and increased international collaboration

R Grol*,[1], FA Cluzeau[2] and JS Burgers[1]

[1]University Medical Centre Nijmegen, Nijmegen, The Netherlands; [2]St George's Hospital Medical School, London, UK

British Journal of Cancer (2003) **89**(Suppl 1), S4–S8. doi:10.1038/sj.bjc.6601077 www.bjcancer.com

Keywords: practice guidelines; quality assessment; international network

The AGREE Collaboration has developed a series of criteria through an EU-funded research project.

The AGREE Instrument (1)

Table I The AGREE instrument

Scope and purpose

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

Stakeholder involvement

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. The guideline has been piloted among target users

Rigour of development

8. Systematic methods were used to search for evidence
9. The criteria for selecting the 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

The AGREE Instrument (2)

Clarity and presentation

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

Applicability

19. The potential organisational barriers in applying the recommendations have been discussed
20. The potential cost implications of applying the recommendations have been considered
21. The guidelines present key review criteria for monitoring and/or audit purposes

Editorial independence

22. The guideline is editorially independent from the funding body
23. Conflicts of interest of guideline development members have been recorded

Using the The AGREE Instrument for CAP guidelines

Researcher initials	
Guideline acronym	

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Fill ONE appropriate column
+ = full agreement
+/- = fair agreement

criteria	YES	NO	?
1			
2			
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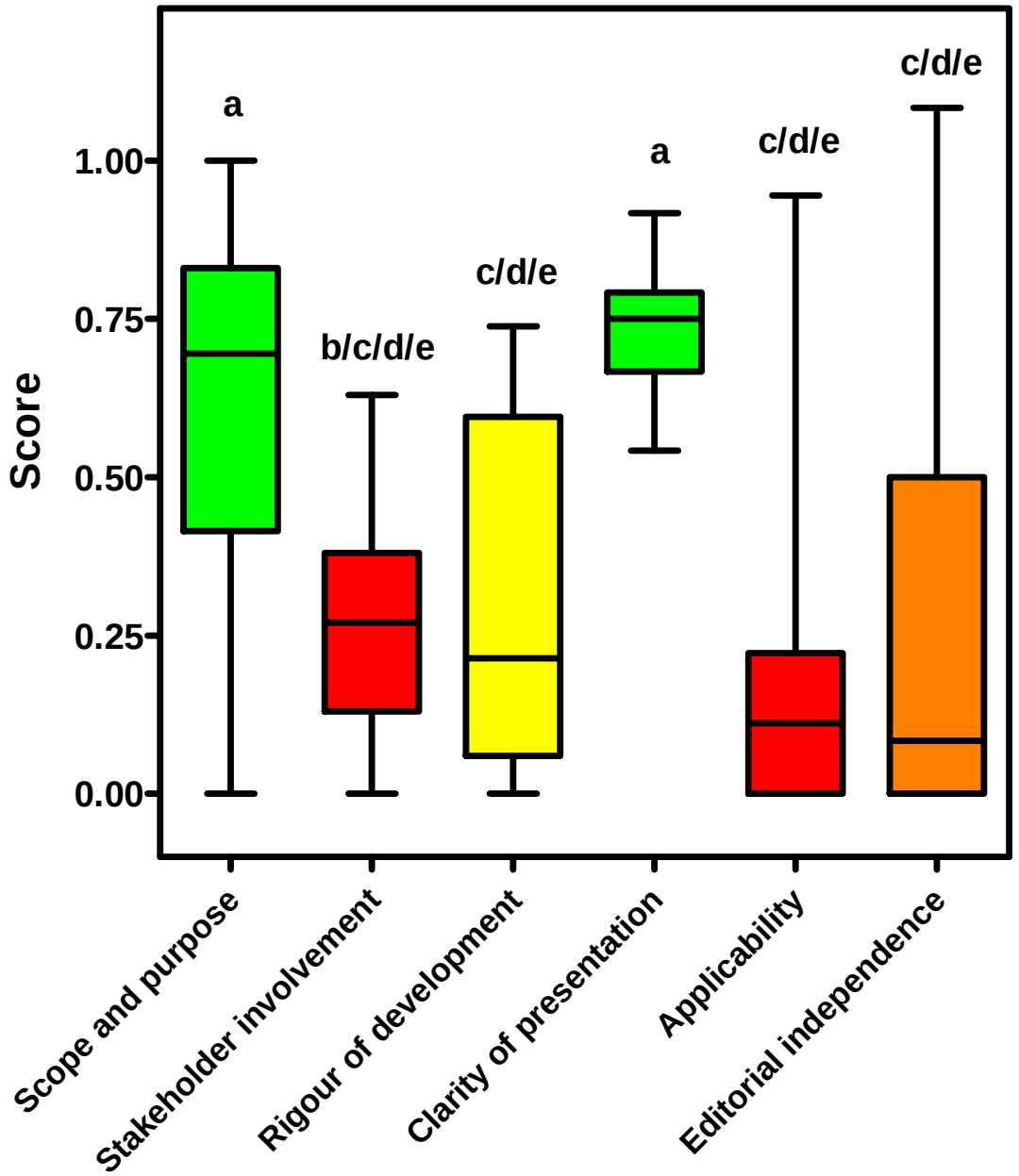
Analysis of 30 CAP guidelines with the AGREE Instrument



Mean scores presented as "boxes and whiskers" (lowest to highest with 25 -75 % and median.
Scores of domains with different letters are significantly different from each other (Kruskal-Wallis test with Dunn's Multiple Comparison Test)

Limitations in daily practice: an example with GP's

- lack of involvement of stakeholders and lack of applicability: analysis of the compliance to a guideline by GP's using the "Lot Quality Assurance Sampling approach" (in-depth interview)

Indication	Introductory comment	1st line treatment	2d line (and condition)
acute RTI (adult *****)	- Acute bronchitis: an antibiotic is not indicated - Community acquired pneumonia: antibiotic (oral) if lethal risk is low (otherwise, hospitalization is required)	- without co-morbidity: amoxicillin - with co-morbidity: amoxicillin-clavulanic acid (if no improvement after 48 h, add a macrolide)	- if non-IgE-mediated allergy to penicillin: cefuroxime axetil - if type I allergy to penicillin moxifloxacin
COPD exacerbation	An antibiotic is, generally speaking, not indicated except for patients with fever (> 38°C), VEMs < 30% of normal values, alteration of the general status and/or no improvement of a non-antibiotic treatment within 4 days in non severe or 3 days in severe exacerbations	- amoxicillin - with co-morbidity: amoxicllin-clavulanic acid (if no improvement after 48 h, replace amoxicillin by amoxicillin-clavulanic acid)	- if non-IgE-mediated allergy to penicillin: cefuroxime axetil - if type I allergy to penicillin moxifloxacin

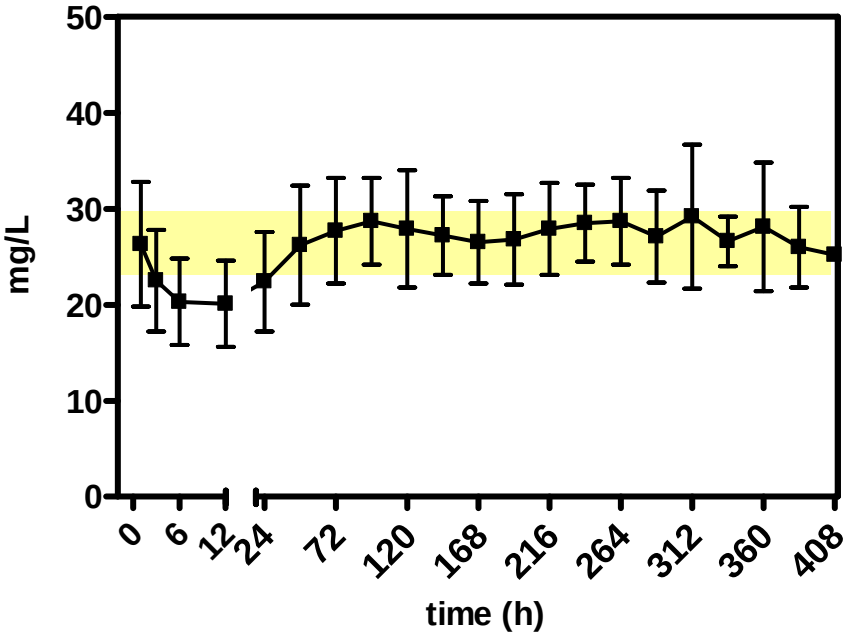
Limitations in daily practice: an example with GP's

- main medical reasons for not following the guidelines shown on the previous slide (LQAS; n=30)

Subcategory	Specific reason(s) mentioned (by order of decreasing number of occurences) *
- perceived severity of the disease or disease considered as requiring antibiotic treatment	- duration/worsening of the symptoms (21) - worsening of the general status (19) - local signs of severity (15) (throat, ear, sinus, ganglions, amygdale; severe discharge) - overall suggestive clinical examination (10) - pain (9) - fever (7) - coloured / abnormal sputum (6) - presentation similar to a recent infection successfully treated with an antibiotic (5) - uncertainty upon auscultation (4) - previous treatment ineffective (3) [1] - dyspnoea (2) - familial epidemic (2) - certainty of a bacterial infection (1)
- fragility of the patient or whit risk	- objectively frail patient (13) (aged, child, overall status or concurrent immunosuppressive medication) - general medical history (personal or familial) (11) - established co-morbidity (6) - COPD patient (5) - risk of bacterial surinfection (3) - smoker (2) - patient not previously known by the prescriber (1)
- uncertainty of the etiological diagnostic	- while waiting for the microbiological results (2) - suspicion of organism causing atypical pneumonia (1) - diagnostic uncertain and possibly worse than thought (1)

Limitations in daily practice: an example with vancomycin

continuous infusion of vancomycin with target set at 27 mg/L



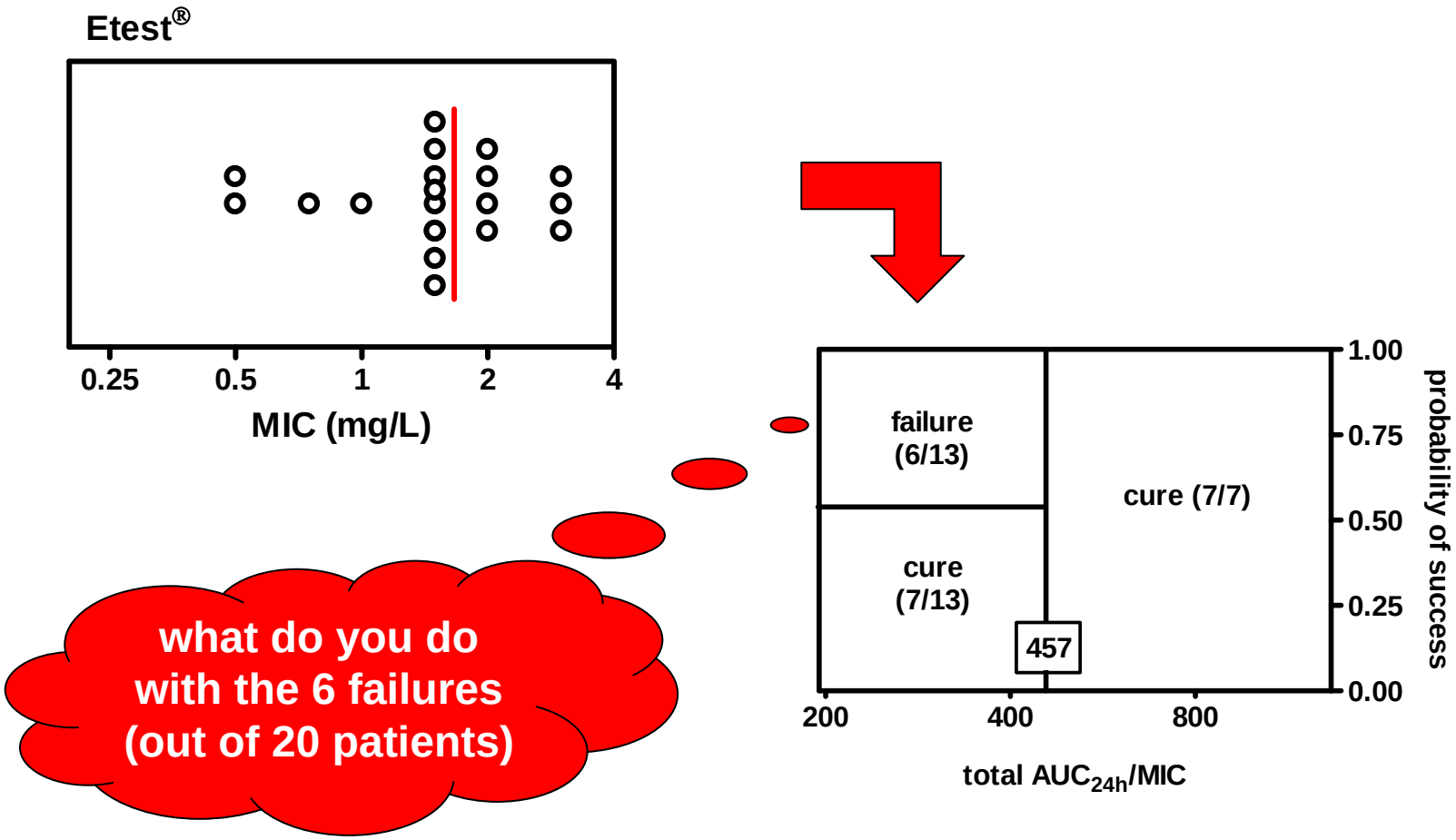
Ampe et al.
in preparation

V for vancomycin ! *

* copied from A. McGowan

should cover to 1.5 mg/L (AUC_{24h} = 27 x 24 = 648)

Limitations in daily practice: an example with vancomycin

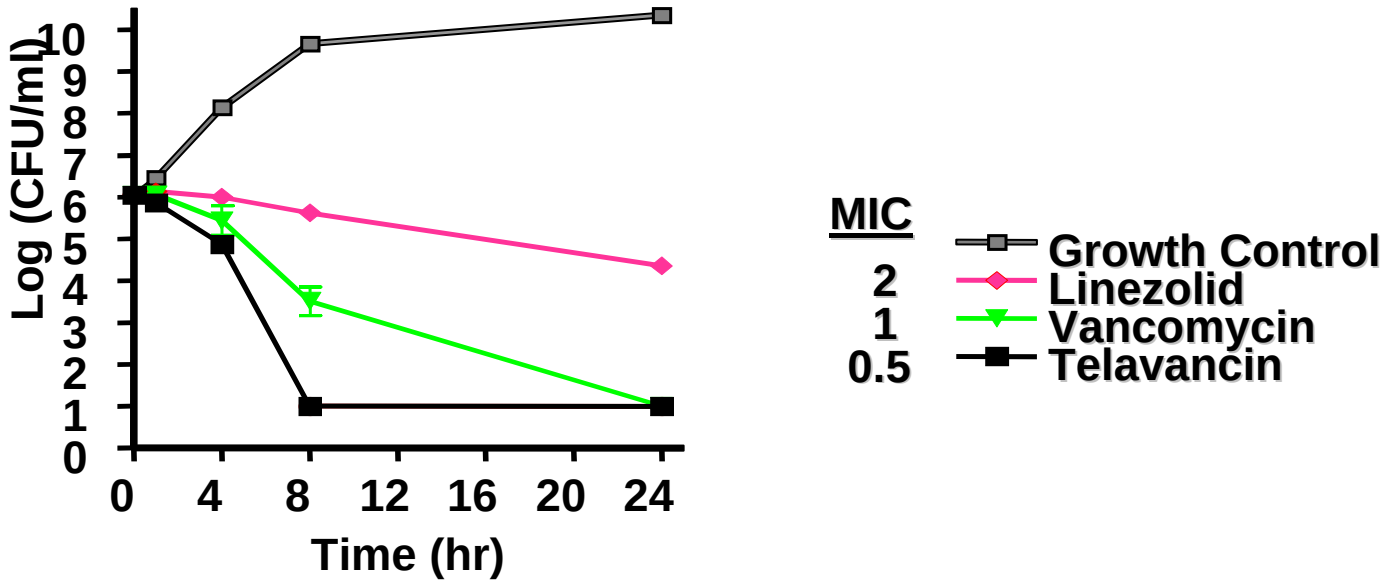


* using microdilution would put the boundary at an AUC/MIC of 650, with failures for MIC > 1.5 mg/L

Guidelines and innovation

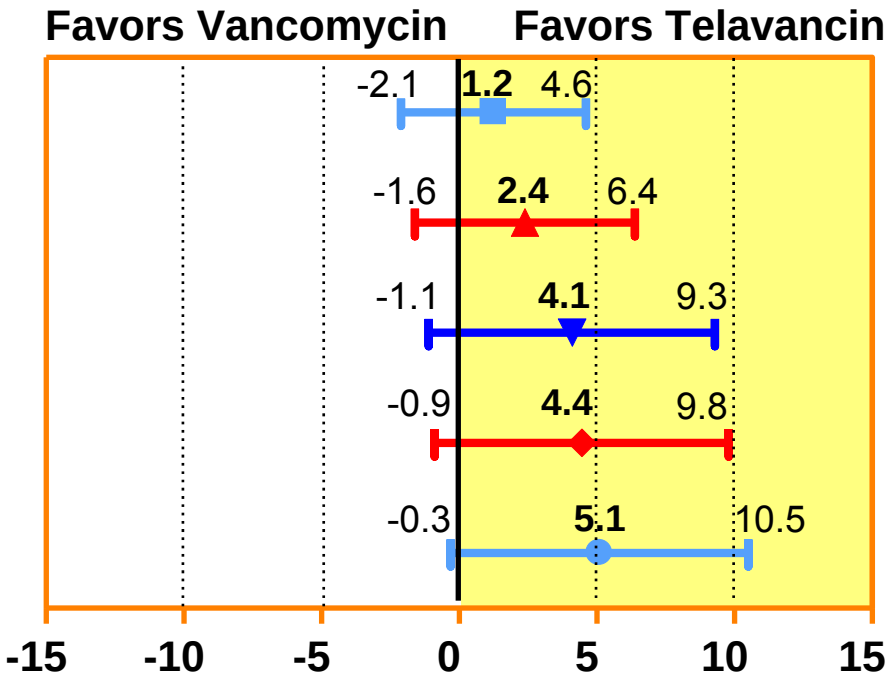
- if guidelines allow for a fully satisfactory treatment, we need no innovation…
- but what if innovation fills up an unmet need ?
- the problem will be the **market anticipated** by the discoverer for the innovation … but…
- in Infectious Diseases, the "unmet need" is infections caused by resistant organisms, which, hopefully, is a small market…
- as a consequence, either
  - novel antibiotics MUST be expensive, or
  - their "too large" promotion (beyond resistant organisms) will clash with guidelines…

Guidelines and innovation



Pace et al. (2003). AAC 47:3602

Guidelines and Innovation



(TLV - VAN, %) with 95% Confidence Interval

	TLV	VAN
Clinical Response in CE Patients	88.3 % (745)	87.1 % (744)
Overall Therapeutic Response in ME Patients	88.6 % (527)	86.2 % (536)
Clinical Response in MRSA	90.6 % (278)	86.4 % (301)
Microbiological Eradication in MRSA	89.9 % (278)	85.4 % (301)
Overall Therapeutic Response in MRSA	89.9 % (278)	84.7 % (301)

Atlas

How would you put this in guidelines ?

Guidelines and Innovation

- Can novel antibiotics be limited in use and be part of the guidelines for situations when the other fail ?
- Yes if
  - they are discovered and developed for cheap …
  - their discovery/development uses other resources than those usually devoted by Industry for these tasks (e.g. tuberculosis…)
  - they do what anticancer drugs have been doing…

"Best treatment" acquisition costs

- **for CAP: 200 euros**
- **one year survival from cancer: 2,000 to > 20,000 euros**

Conclusions

- Guidelines are interesting and most probably useful
- Their writing is a difficult exercise
- Their implementation is a long journey not without surprise
- They must remain open to accommodate for special situations and innovation
- Without that, they may create problems.