

Guidelines in infectious diseases: from diversity to logics (a study about CAP guidelines)



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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 ?
- To a conclusion ...



**the case of
the CAP
guidelines**

Guidelines: origin, basis and use

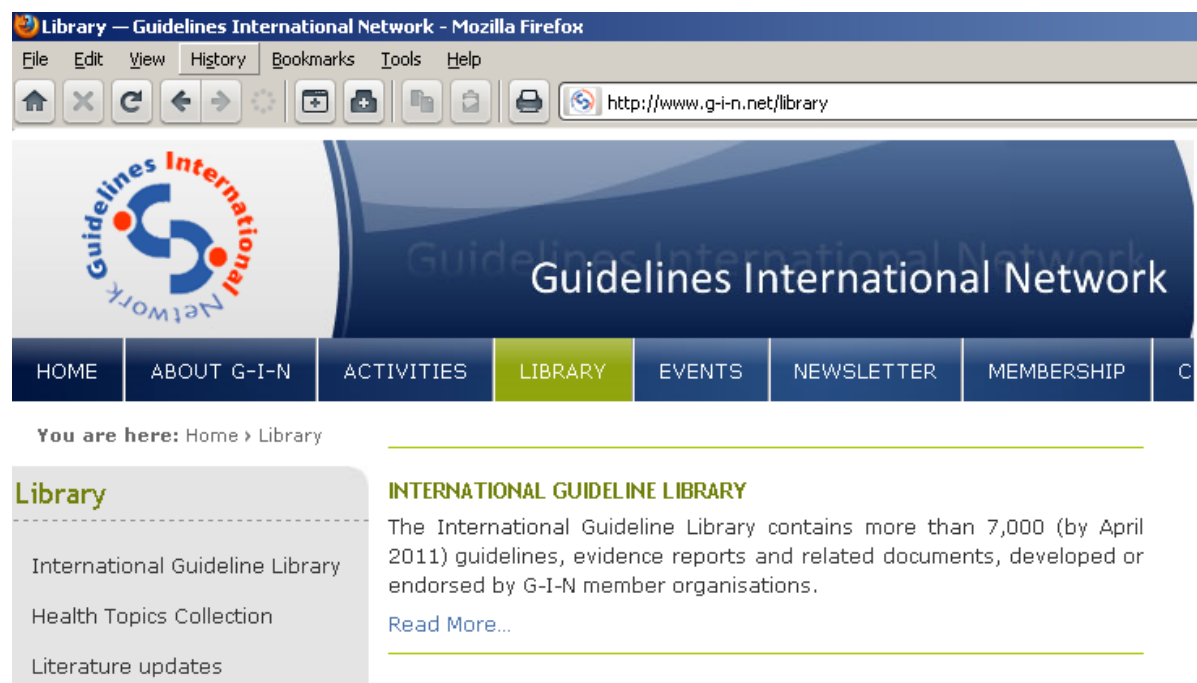
- Clinical guideline aim at **guiding decisions and criteria** regarding diagnosis, management, and treatment
- Guidelines have been used since the beginning of Medicine
- Modern medical guidelines are supposed to be based on **critical examination of current evidence**, with emphasis on **evidence-based** 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: in the community

BMC Family Practice



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: in hospital

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 Witte², Willy E. Peetermans³, Steven Simoons¹ and Gert Laekeman¹

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.

Guidelines: are they used?

Example 3: are they used in the patients you really see ?

Reasons Why Emergency Department Providers Do Not Rely on the Pneumonia Severity Index to Determine the Initial Site of Treatment for Patients with Pneumonia

Drahomir Aujesky,¹ Julie B. McCausland,² Jeff Whittle,⁵ D. Scott Obrosky,^{3,4} Donald M. Yealy,² and Michael J. Fine^{3,4}

¹Division of General Internal Medicine, Department of Medicine, University of Lausanne, Lausanne, Switzerland; ²Department of Emergency Medicine, ³Division of General Internal Medicine, Department of Medicine, University of Pittsburgh, and ⁴Veterans Affairs Center for Health Equity Research and Promotion, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania; ⁵Primary Care Division, Clement J. Zablocki Veterans Affairs Medical Center and Division of General Internal Medicine, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin.

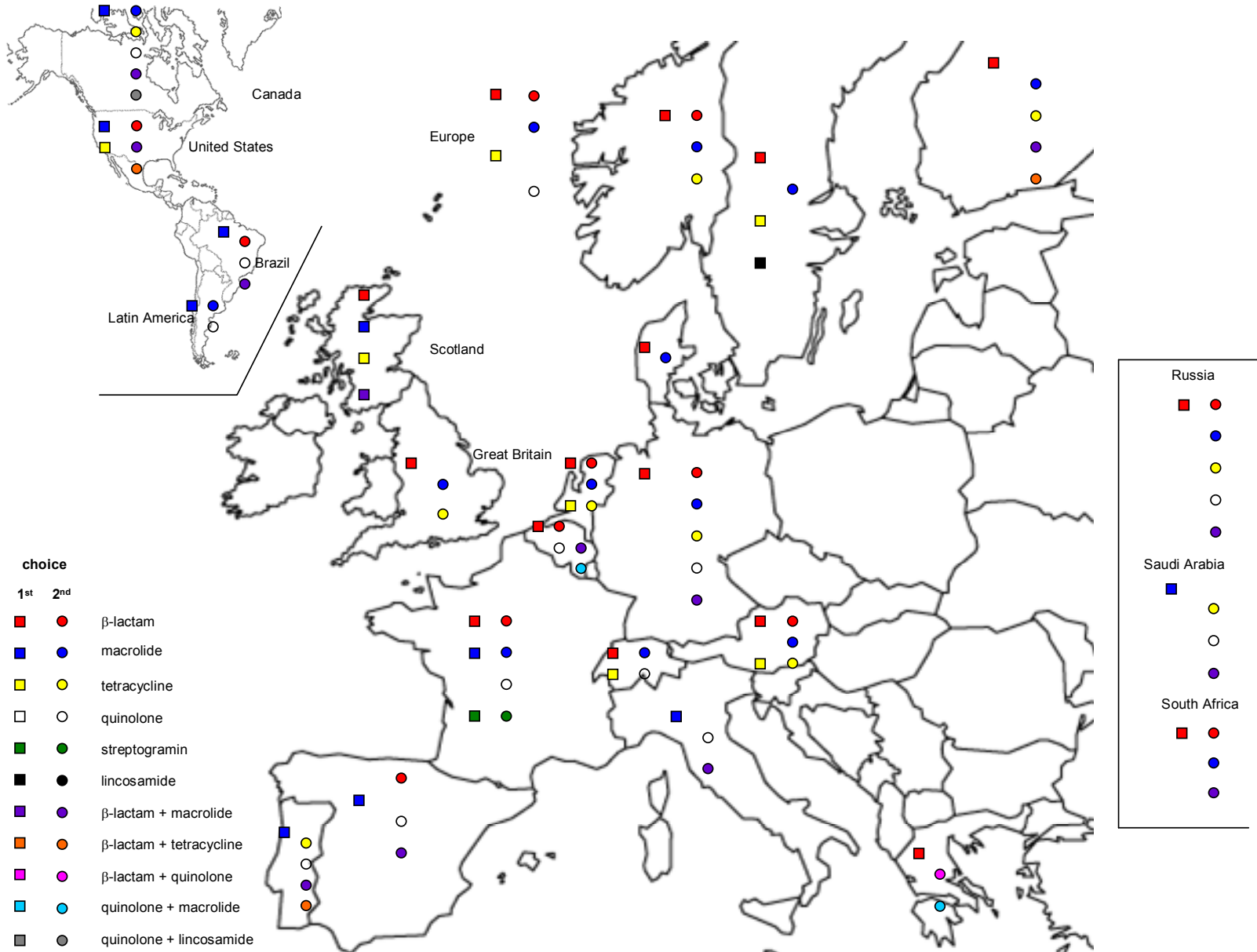
ED providers reported that, in most instances, they overrode guideline recommendations because of specific clinical factors, many guideline-discordant decisions were based on patient, family, or physician requests, or because physicians subjectively judged the case of CAP to be more or less severe than suggested by the PSI. Additional educational efforts and/or alternative guideline implementation strategies may be able to further safely reduce the proportion of guideline-discordant site-of-treatment decisions for patients with CAP.

guidelines based on disease analysis only may not tell the whole story

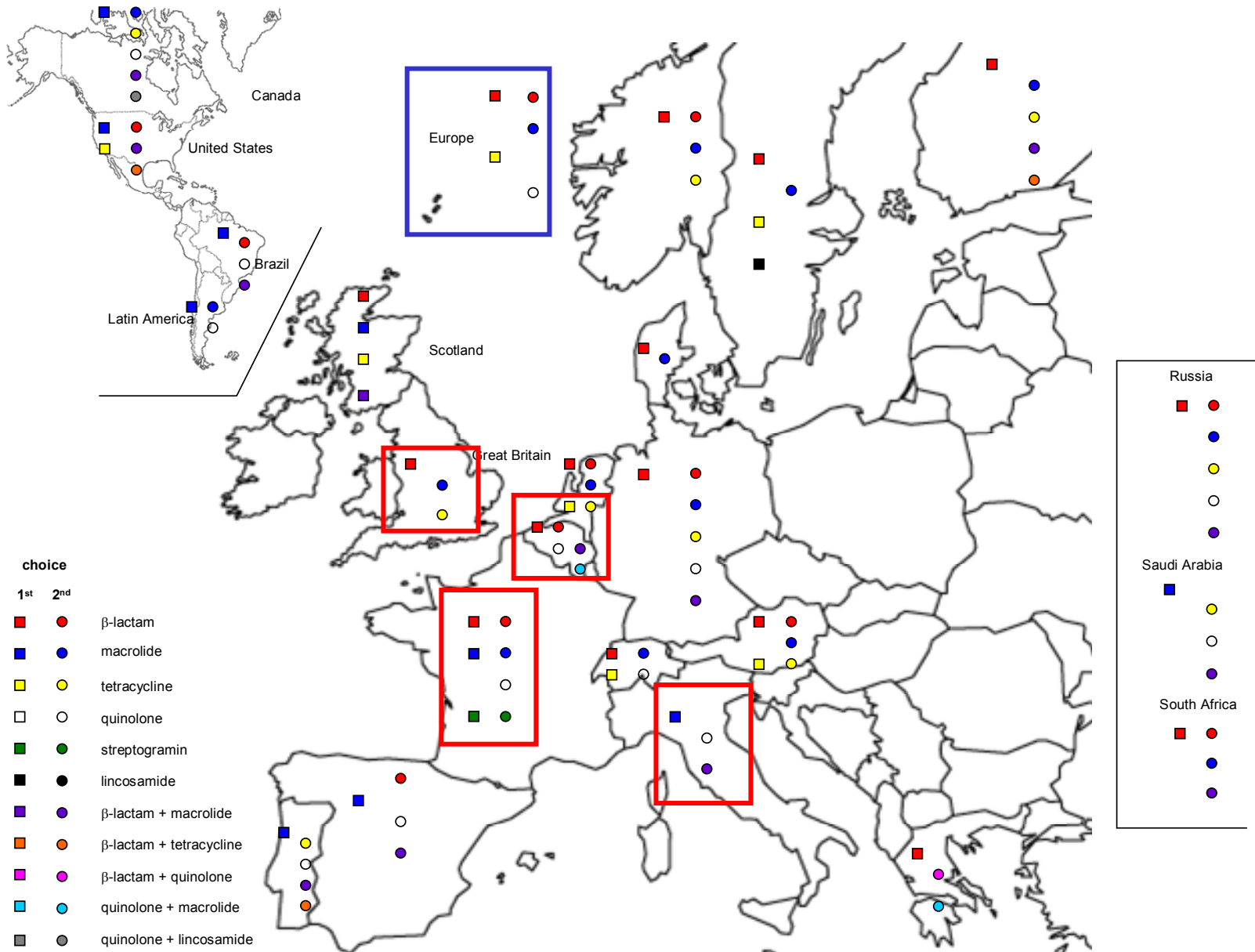
Guidelines: are they homogenous ?

- 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 than what may be anticipated from the above considerations...

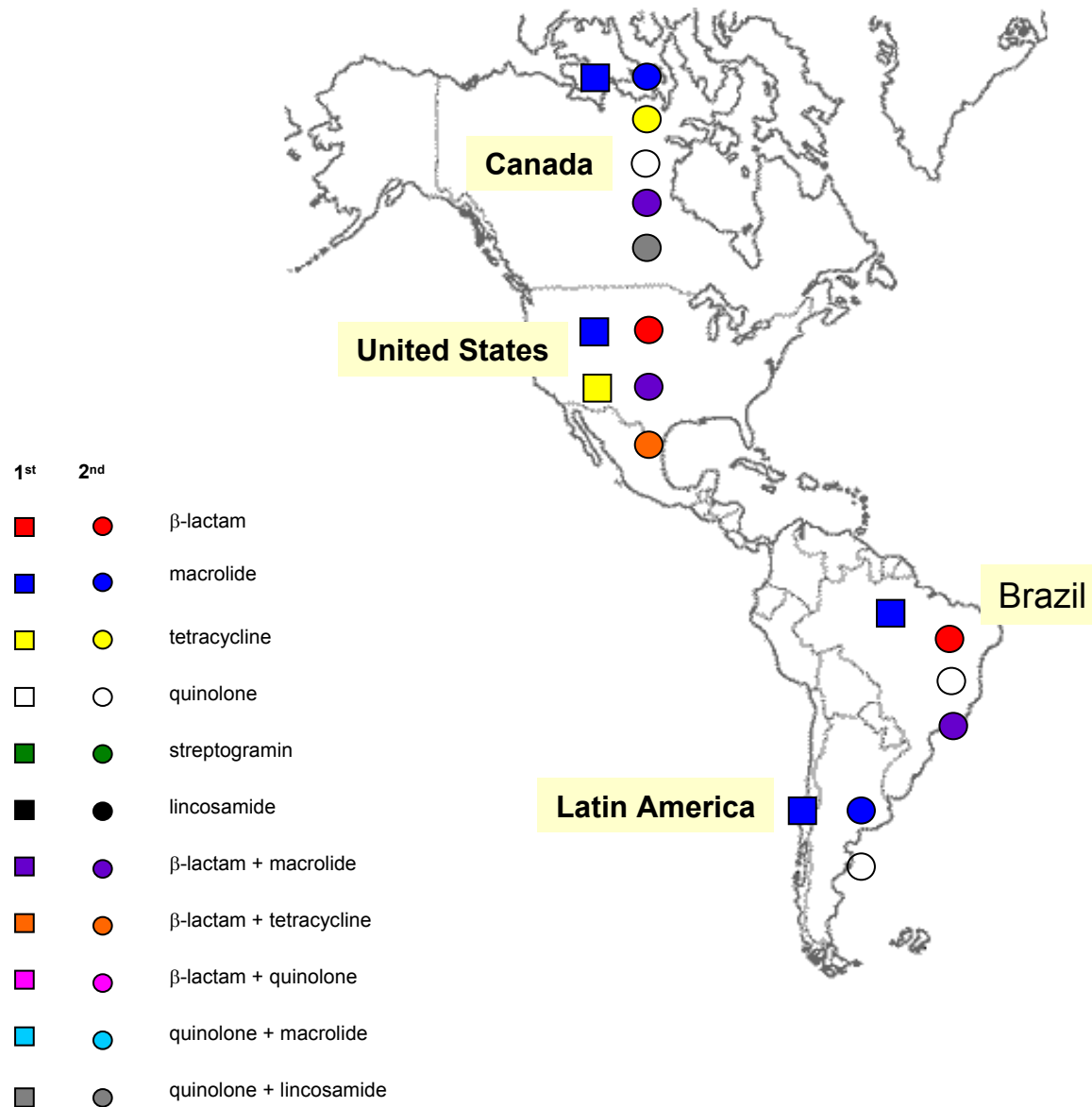
CAP Guidelines: many variations



CAP Guidelines: variations in Europe



CAP Guidelines: situations in Americas



A (short) * summary of variations ...

+ = 1st line (+) = alternative

Organization ^a (country or region)	β-lactam ^b	macrolide	tetracycl.	quinolone ^c	strepto- gramin ^d	β-lactam + macrolide	β-lactam + tetracycl.
ERS/ESCMID Europe **	+ (+)	(+)	+	(+)			
AFSSAPS France	+ (+)	+ (+)		(+)	+ (+)		
BTS Great Britain	+	(+)	(+)				
PESC/GRS/GSI/CAPNE TZ Germany	+ (+)	(+)	(+)	(+)		(+)	
SEPAR Spain	(+)	+		(+)		(+)	
SPP Portugal		+	(+)	(+)		(+)	(+)
IDSA/ATS United States	(+)	+	+	(+)		(+)	(+)
ALAT Latin America		+ (+)		(+)			
BTA Brazil	(+)	+		(+)		(+)	

* the full list (30 guidelines) is available upon request

^a see back-up slides for definition of acronyms

^b amoxicillin most often cited

^c levofloxacin or moxifloxacin

^d pristinamycin




** the ERS/ESCMID guideline revised in 2011 states that

- the prevalence of resistance to penicillin and other drugs has considerably complicated the empirical treatment
- the daily dose of penicillin can be up to 12 g (in 6 administrations) for organisms with an MIC ≤ 8 mg/L;

Questions to ask when setting guidelines in infectious diseases (with application to CAP)

- How sure are you of the diagnostic ?
- **Which are the main pathogens and their current resistance patterns ?**
- How should the therapy be initiated (empiric vs. directed)
- **Which level of side effect do you accept ?**
- **Which patients do you mainly treat ?**
- Do cost matter ?
- Which are your real choices ?

Main pathogen (a short view)

Pathogen	Frequency (%)	
	from Woodhead (2002) means of 41 studies	from Woodhead (2011) range of 17 studies
No pathogen identified	49.8	22.2 – 63.8
<i>Streptococcus pneumoniae</i>	19.3	0 - 36 
Viruses (incl. Influenza)	11.7	2 - 33
<i>Mycoplasma pneumoniae</i>	11.1	0 - 3 
<i>Chlamydia pneumoniae</i>	8.0	7 - 37
<i>Haemophilus influenzae</i>	3.3	0 - 14
<i>Legionella spp</i>	1.9	0 - 13 
Other organisms	1.6	
<i>Chlamydia psittaci</i>	1.5	0 - 9
<i>Coxiella burnetii</i>	0.9	0 - 3
<i>Moraxella catarrhalis</i>	0.5	0 - 3
Gram-negative enteric bacteria	0.4	0 - 1
<i>Staphylococcus aureus</i>	0.2	0 - 1

- Woodhead M. Community-acquired pneumonia in Europe: causative pathogens and resistance patterns. Eur Respir J Suppl 2002; 36, 20s-7s.
- Woodhead M, Blasi F, Ewig S et al. Guidelines for the management of adult lower respiratory tract infections--full version. Clin Microbiol Infect 2011; 17 Suppl 6, E1-59.

Main pathogens: the reality ...

Outpatient, no cardiopulmonary disease or modifying factors	<i>Streptococcus pneumoniae</i> , <i>Mycoplasma pneumoniae</i> , <i>Chlamydophila pneumoniae</i> (alone or as mixed infection), <i>Haemophilus influenzae</i> , respiratory viruses, others (<i>Legionella</i> spp., <i>Mycobacterium tuberculosis</i> , endemic fungi)
Outpatient, with cardiopulmonary disease and/or modifying factors, or HCAP with no resistance risk factors	All of the above plus drug-resistant <i>Streptococcus pneumoniae</i> , enteric Gram-negatives and possibly anaerobes (with aspiration)
Inpatient, with cardiopulmonary disease and/or modifying factors, or HCAP with no resistance risk factors	<i>Streptococcus pneumoniae</i> (including resistant), <i>H. influenzae</i> , <i>Mycoplasma pneumoniae</i> , <i>C. pneumoniae</i> , mixed infection (bacteria plus atypical pathogen), enteric Gram-negatives, anaerobes (aspiration), viruses, <i>Legionella</i> spp., others (<i>Mycobacterium tuberculosis</i> , endemic fungi, <i>Pneumocystis jirovecii</i>)
Inpatient, with no cardiopulmonary disease or modifying factors	All of the above, but resistant S.p. and enteric Gram-negatives are unlikely
Severe CAP, with no risks for <i>Pseudomonas aeruginosa</i>	<i>Streptococcus pneumoniae</i> (including resistant), <i>Legionella</i> spp., <i>H. influenzae</i> , enteric Gram-negative bacilli, <i>Staphylococcus aureus</i> , <i>Mycoplasma pneumoniae</i> , respiratory viruses, others (<i>C. pneumoniae</i> , <i>Mycobacterium tuberculosis</i> , endemic fungi)
Severe CAP, with risks for <i>P. aeruginosa</i> , or HCAP with resistance risk factors	All of the above pathogens, plus <i>P. aeruginosa</i>

Which resistance ?

Organisms	Antibiotic class	Main mechanism	Clinical consequence
<i>S. pneumoniae</i>	β -lactams (pénicillins/ cephalosporins...)	altered sequence in PBPs (2B, 2X, 1A; mosaic genes) with progressive increase in MIC	"intermediate" isolates still clinically susceptible with increase of dose and frequency of administration
	macrolides, tetracyclines, fluroquinolones	efflux (<i>mefA</i>)	intermediate (but ...)
		target alteration (<i>ermB</i>)	full resistance
<i>H. influenzae</i> *	β -lactams	β -lactamase	full resistance (reversed by clavul. acid)
		alteration of PBPs	increase in MIC (clinically rare)
<i>Mycoplasma</i>, <i>Chlamydia</i>, <i>Legionella</i> **	macrolides fluroquinolones	target alteration (ribosomal / gyrase)	full resistance (clinically rare / exceptional)

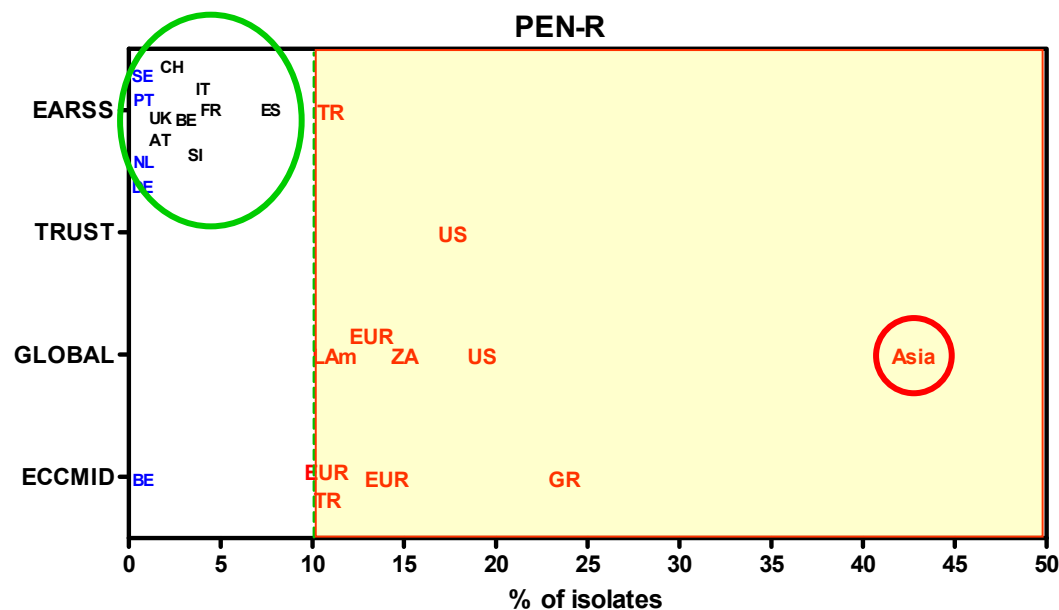
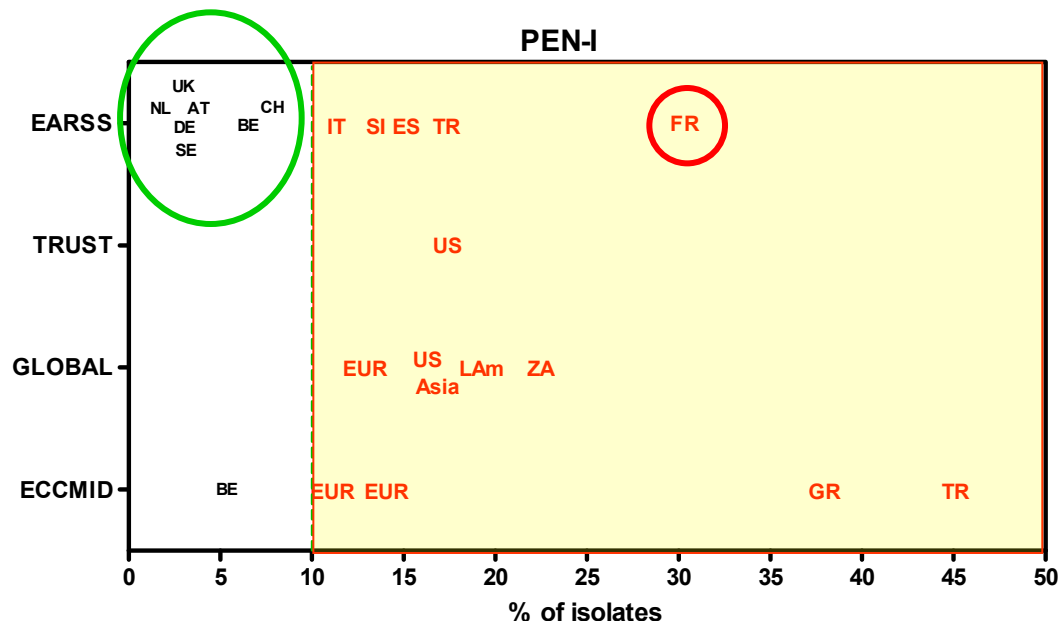
* macrolides are poorly active against *H. influenzae* (no EUCAST breakpoint)

** β -lactams are intrinsically poorly active against *Mycoplasma* and *Chlamydia* and poorly active against *Legionella* is because of its intracellular character

Resistance of *S. pneumoniae* *

*analysis of resistance to penicillins (with CAP as main indication) in 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



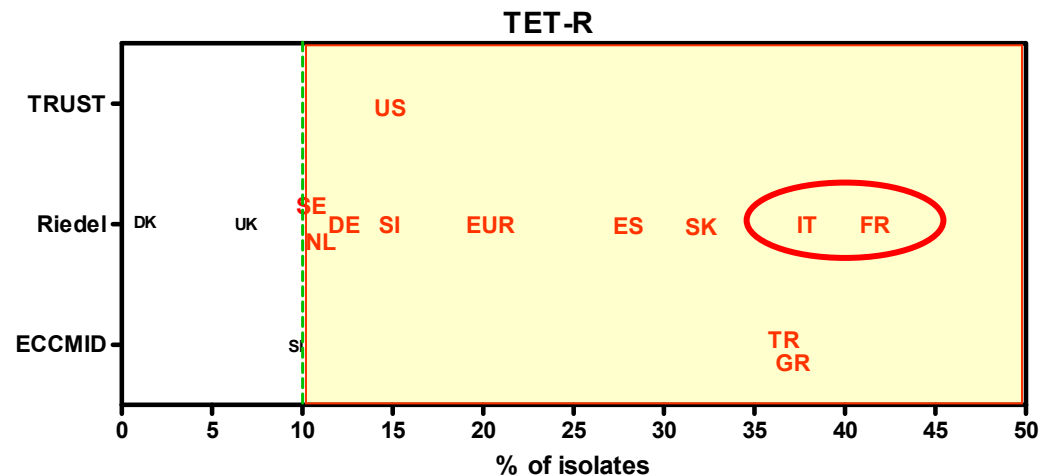
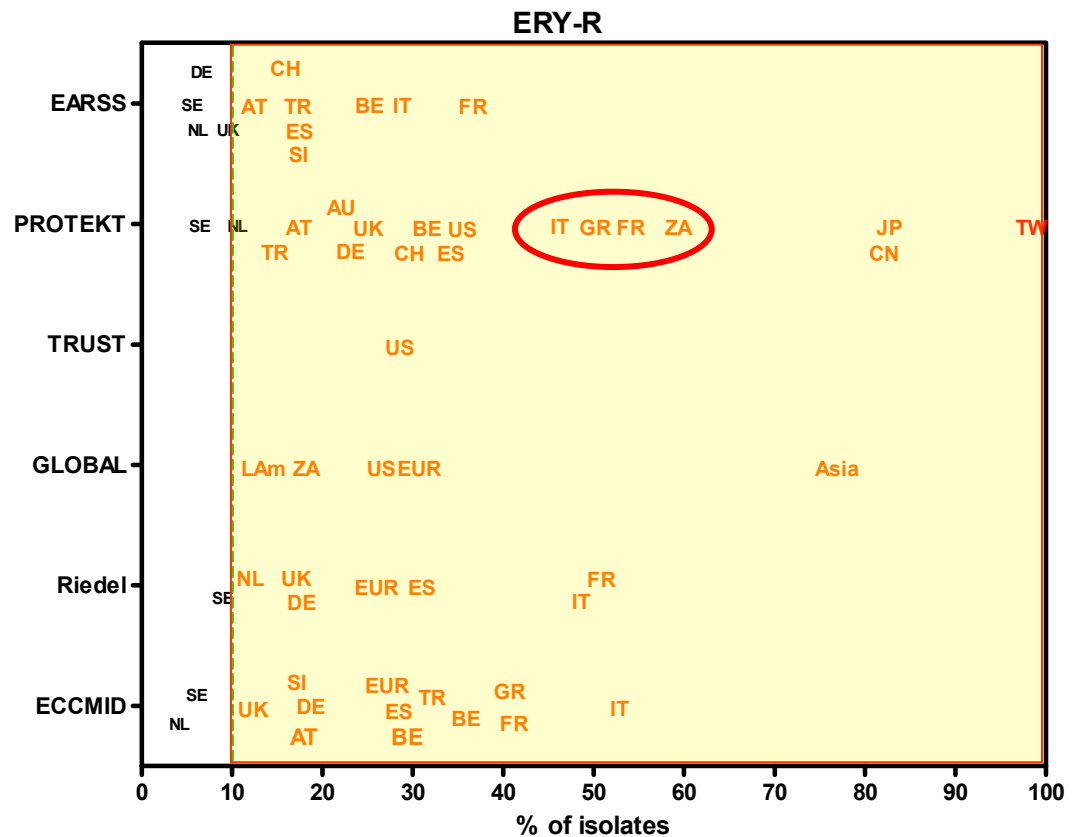
Carbonnelle *et al.*, in preparation

Resistance of *S. pneumoniae* *

*analysis of resistance of erythromycin and doxycycline (with CAP as main indication) in surveillance systems or publications (*S. pneumoniae*)

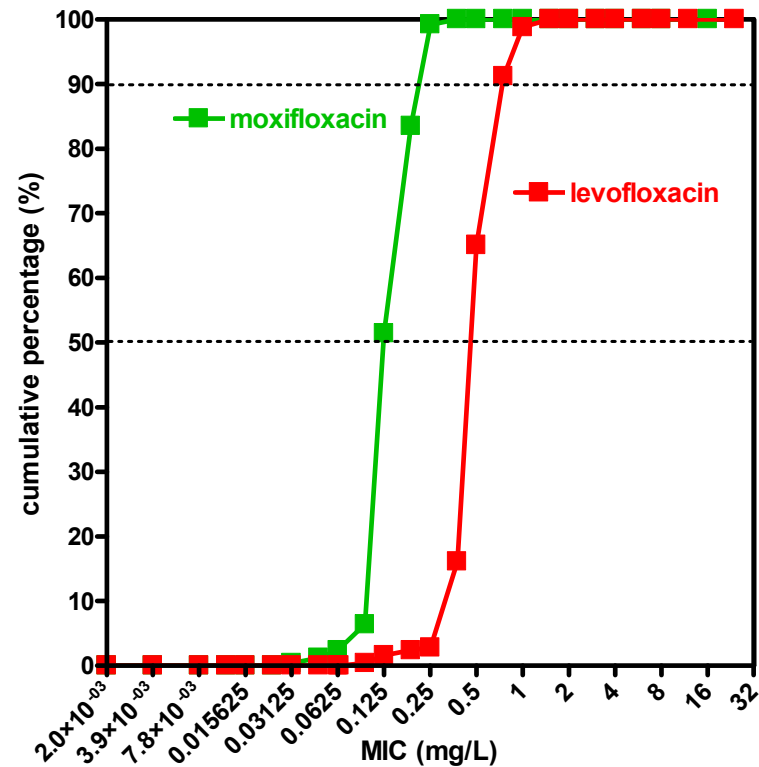
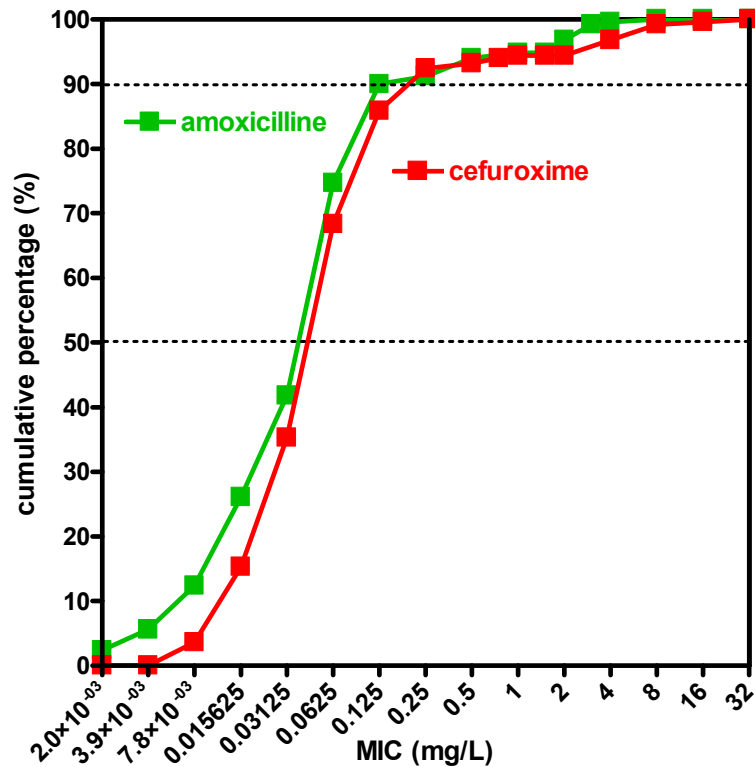
- **EARSS**: European Antimicrobial Surveillance system
- **PROTEKT**: Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin
- **TRUST**: Tracking Resistance in the United States Today
- **GLOBAL**: Global Landscape On the Bactericidal Activity of Levofloxacin
- **Riedel**: Eur J Clin Microbiol Infect Dis. 2007 Jul;26(7):485-90.
- **ECCMID**: abstracts of the 18th European Congress of Clinical Microbiology and Infectious Diseases

Carbonnelle *et al.*, in preparation



The message : know YOUR resistance pattern ... by means of MIC distributions...

I'll come to
breakpoints later



But breakpoints use may also be important: An example of "improvement" in Latin America...

Table 1 - Penicillin-resistance rates according to the 2007 CLSI and 2008 CLSI standards in pneumococcal strains collected from children hospitalized with pneumonia (1999 to 2008)

Resistance	n*	%	n [†]	%
Intermediate	22	22	1	1
Full	11	11	0	0
Total [‡]	33	33	1	1

CLSI = Clinical and Laboratory Standards Institute.

* According to the 2007 CLSI standard.

† According to the CLSI 2008 standard.

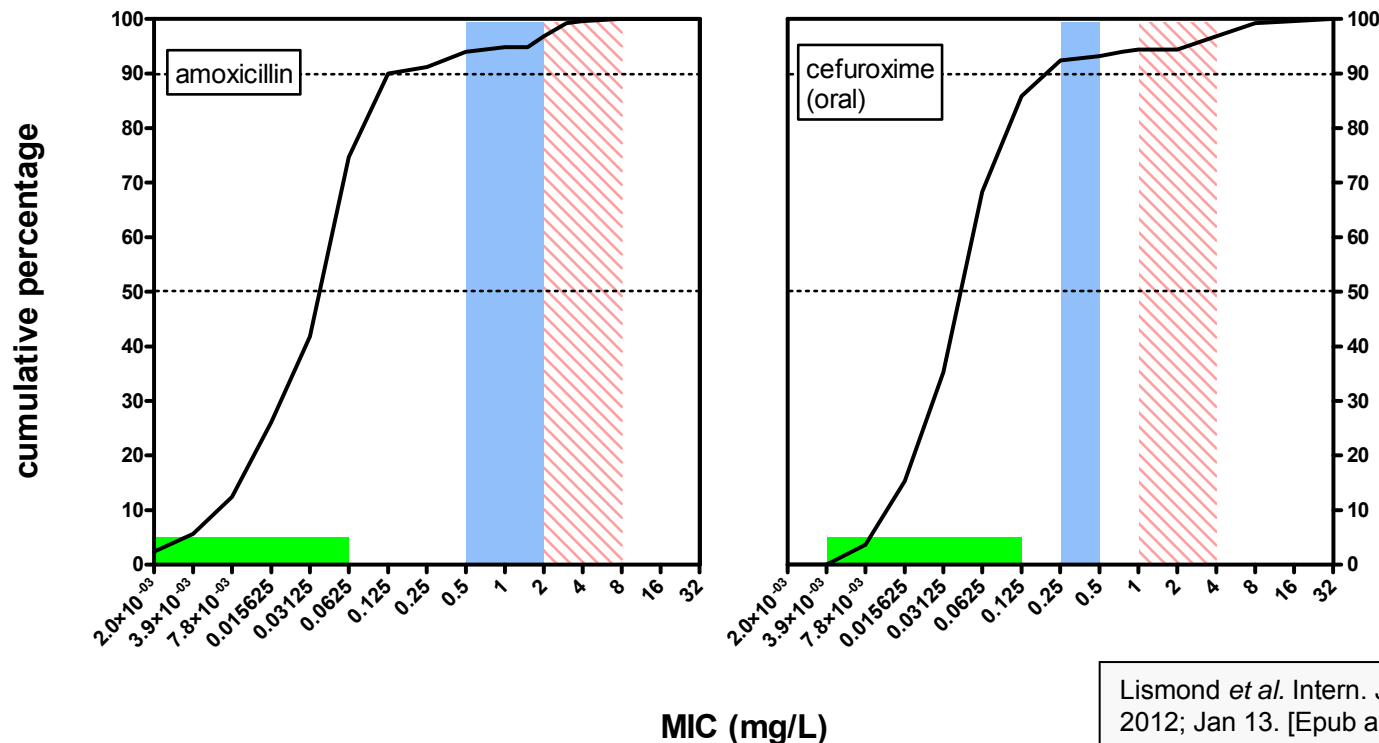
‡ Total of 100 strains analyzed.

2007: S: ≤ 0.06, I: 0.12 to 1, R > 2 µg/mL
2008: S: ≤ 2 I: 4 to 8, R ≥ 8 µg/mL

Wolkers PC, Mantese OC, Paula A, Almeida VV, Aguiar PA, Alvares JR, Almeida SC, Brandileone MC. New susceptibility breakpoints in antimicrobial resistance rates of invasive pneumococcal strains. J Pediatr (Rio J). 2009 Sep-Oct;85(5):421-5.

Breakpoints: EUCAST vs. CLSI for *S. pneumoniae* in Belgium

wild type population (EUCAST)
 clinical breakpoint: EUCAST
 CLSI

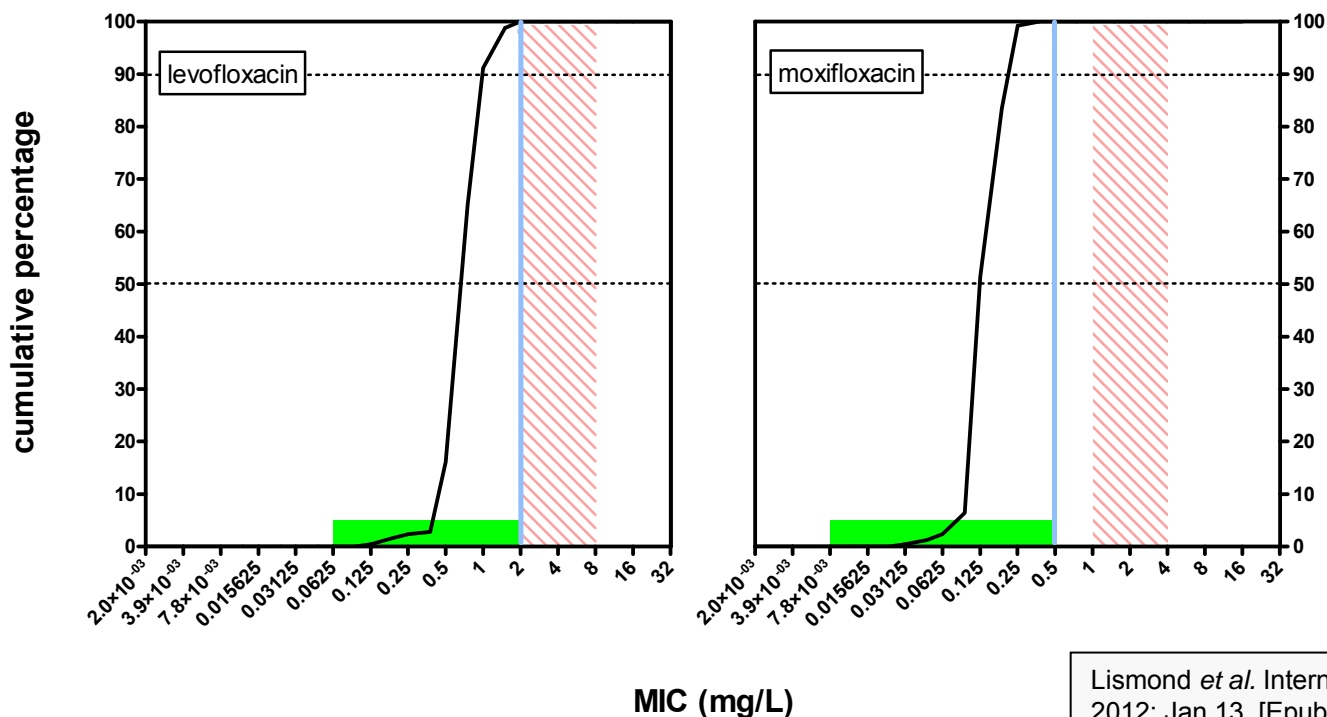


Lismond *et al.* Intern. J. Antimicrob. Ag.
 2012; Jan 13. [Epub ahead of print]

Comments:

- for amoxicillin: With the new [CLSI] definitions of resistance [for *S. pneumoniae*], very few pathogens will be defined as resistant; however, those that are may affect outcome. **In fact, most experts believe that CAP caused by organisms with a penicillin MIC of ≥ 4 mg/L, still an uncommon finding, can lead to an increased risk of death.**
 Ref. and Feikin *et al.* *Am J Public Health* 2000; 90:223-229.
- for ceftriaxone: because of its poor bioavailability, EUCAST breakpoint is lower ... and shows the limits...

Breakpoints: EUCAST vs. CLSI for *S. pneumoniae* in Belgium



Lismond *et al.* Intern. J. Antimicrob. Ag. 2012; Jan 13. [Epub ahead of print]

Comment: With the new [CLSI] definitions of resistance [for *S. pneumoniae*], levofloxacin is perfect, but with the EUCAST breakpoint, it cleraly "knocks the wall". **In fact, EUCAST will recommend a "high dosage" of levofloxacin (2 x 500 mg).** Conversely, even with the severe EUCAST breakpoint (0.5 mg/L !), moxifloxacin is still one dilution lower than its limit. From EUCAST rational document (see <http://www.eucast.org/documents/rd/>)

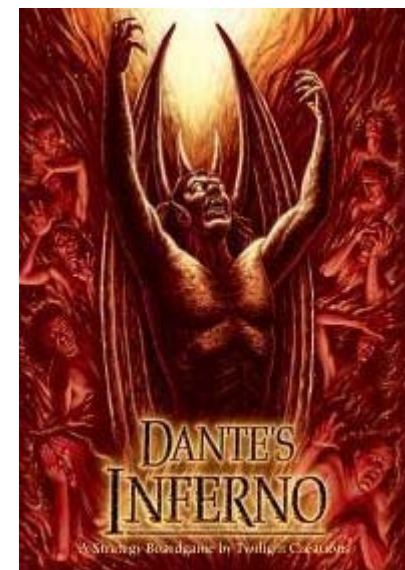
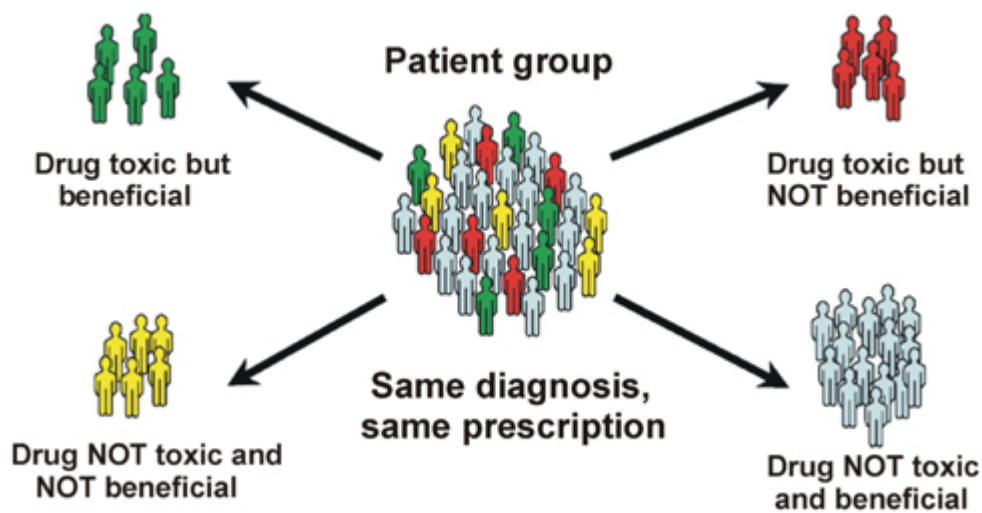
Side effects...



therapy ?



side effects ?



All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
β -lactams	amoxicillin	<ul style="list-style-type: none"> • Anaphylactic reactions • <i>Clostridium difficile</i>-associated colitis • Digestive tract: diarrhoea, nausea • CNS: agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness.
	amoxicillin - clavulanic acid	<ul style="list-style-type: none"> • Anaphylactic reactions • <i>Clostridium difficile</i>-associated colitis • Hepatic toxicity, including hepatitis and cholestatic jaundice • Digestive tract: diarrhoea, nausea • CNS : agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness
	cefuroxime	<ul style="list-style-type: none"> • Anaphylactic reactions and cutaneous eruptions • Nephrotoxicity (aggrav. with loop diuretics) • Hepatic toxicity • <i>Clostridium difficile</i>-associated colitis
	ceftriaxone	<ul style="list-style-type: none"> • Anaphylactic reactions and cutaneous eruptions • Digestive tract: diarrhoea, nausea • <i>Clostridium difficile</i>-associated colitis • Hematologic disturbances (éosinophilia, leucopenia, granulopenia, thrombopenia) • Hepatic and biliary toxicities (precipitation of Ca^{++} salt) • CNS: cephalalgia, vertigo

* based on an analysis of the respective labelling (SmPC or equivalent)

Carbonnelle *et al.*, : "From Pharmacovigilance to Risk Management", 9th IsOP, 2009; and in preparation

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
Macrolides	clarithromycin	<ul style="list-style-type: none"> • Anaphylactic reactions • <i>Clostridium difficile</i>-associated colitis • Drug interactions (CYP450) • Hepatic toxicity, including hepatitis and cholestatic jaundice • Palpitations, arrhythmias including prolonged QTc • Digestive tract: diarrhoea, nausea, vomiting, abnormal taste • CNS: headache, confusion, ...
	azithromycin	<ul style="list-style-type: none"> • Anaphylactic reactions • <i>Clostridium difficile</i>-associated colitis • Drug interactions (CYP450), less frequent than with other macrolides • Hepatic toxicity, including hepatitis and cholestatic jaundice • Digestive tract: diarrhoea, nausea, abdominal pain • CNS: dizziness, fatigue, vertigo, ... • Genitourinary: nephritis, vaginitis
	telithromycin	<ul style="list-style-type: none"> • Anaphylactic reactions and allergic skin reactions • <i>Clostridium difficile</i>-associated colitis • Hepatotoxicity • Visual disturbance • Loss of consciousness • Respiratory failure in patients with myasthenia gravis • QTc prolongation • Drug interactions (CYP450) • Digestive tract: diarrhoea, nausea, vomiting, dysgeusia • CNS: headache, dizziness

* based on an analysis of the respective labelling (SmPC or equivalent)

Carbounelle *et al.*, : "From Pharmacovigilance to Risk Management", 9th IsOP, 2009; and in preparation

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
fluoroquinolones	levofloxacin	<ul style="list-style-type: none"> • Anaphylactic reactions and allergic skin reactions • <i>Clostridium difficile</i>-associated colitis • Hematologic toxicity • Hepatotoxicity • Central nervous system effects: headache, insomnia, dizziness, convulsions • Musculoskeletal: tendinopathies • Peripheral neuropathy • Prolongation of the QTc interval and isolated cases of torsade de pointes • Digestive tract: nausea, diarrhoea
	moxifloxacin	<ul style="list-style-type: none"> • Anaphylactic reactions and allergic skin reactions • <i>Clostridium difficile</i>-associated colitis • Musculoskeletal: Tendinopathies • Peripheral neuropathy • Prolongation of the QT interval • Central nervous system effects: headache, insomnia, dizziness, convulsions • Digestive tract: nausea, diarrhoea

* based on an analysis of the respective labelling (SmPC or equivalent)

Carbonnelle *et al.*, : "From Pharmacovigilance to Risk Management", 9th IsOP, 2009; and in preparation

All antimicrobials have associated risks *



Conclusions (of this part):

- All antimicrobials used in RTI are associated with known toxicities
- The main point will be the recognition of patients at risk (exclusions)
- The next point will be a correct evaluation of the benefit / risk ratio in the specific environment and for the specific patient

Carbonnelle *et al.*, : "From Pharmacovigilance to Risk Management", 9th IsOP, 2009; and in preparation

But, why so much (apparent or real ?) problems in reaching a consensus ?

- Guidelines should take enough parameters into account (qualitatively and quantitatively)... to be pertinent
- Guidelines must linked to a the specific variables of the environment in which they will apply
- Guidelines must be applicable and regularly updated...
- Guidelines should not be recipes...

Editorial

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

R Grol^{*,1}, FA Cluzeau² and JS Burgers¹

¹University Medical Centre Nijmegen, Nijmegen, The Netherlands; ²St 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
© 2003 FNCLCC

Keywords: practice guidelines; quality assessment; international network

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

* "Appraisal of Guidelines Research and Evaluation" -- developed through an EU-funded research project and available on <http://www.agreecollaboration.org/>

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
-

* "Appraisal of Guidelines Research and Evaluation" -- developed through an EU-funded research project and available on <http://www.agreecollaboration.org/>

Using the The AGREE Instrument for CAP guidelines

Researcher initials	
Guideline acronym	

Fill ONE appropriate column + = full agreement +/- = fair agreement			
criteria	YES	NO	?
1			
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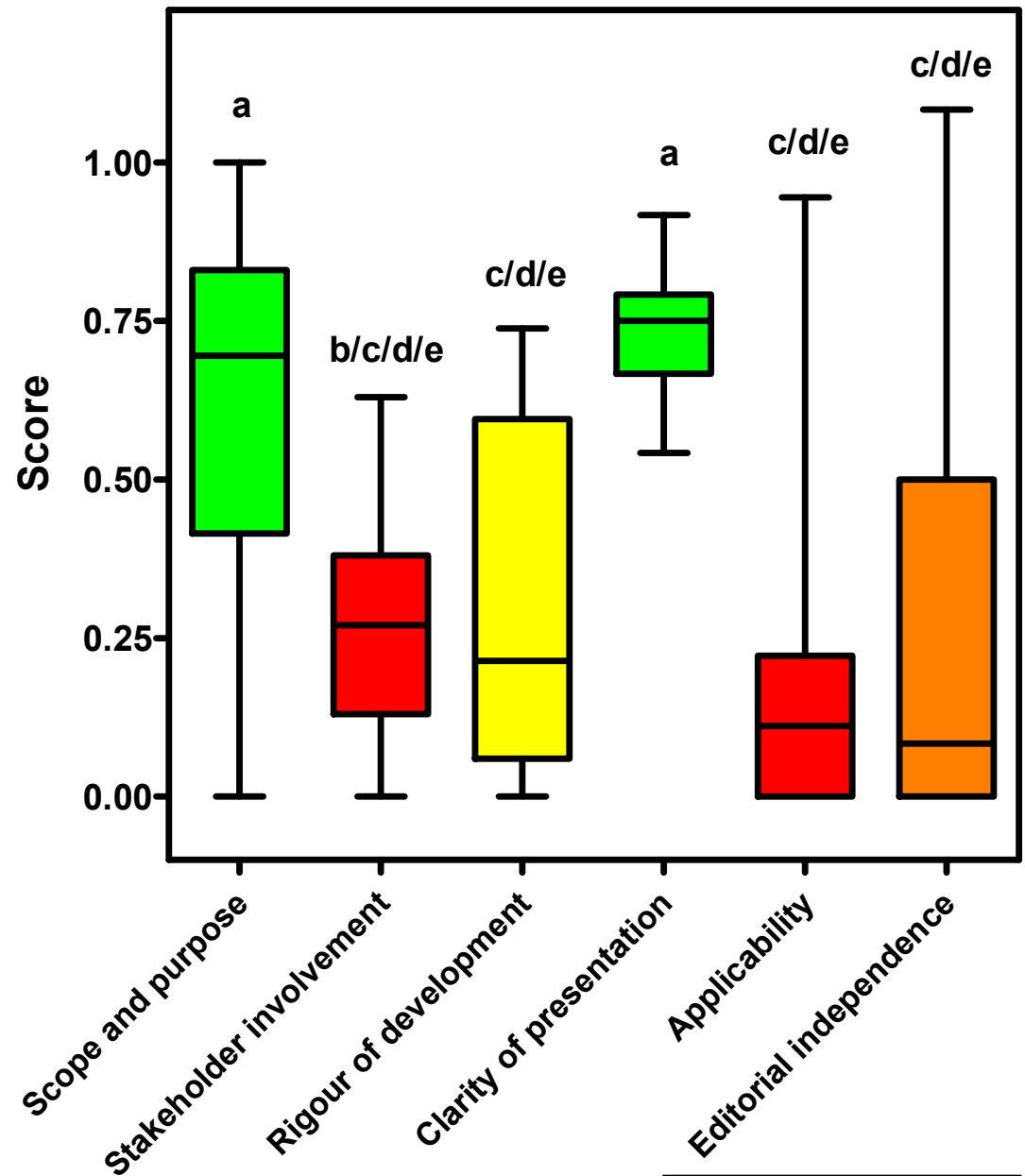
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Analysis of 30 CAP guidelines with the AGREE Instrument

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)



Carbonnelle *et al.*, submitted

A revised AGREE is available

AGREE II: advancing guideline development, reporting and evaluation in health care

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Key points

- AGREE II (Appraisal of Guidelines, Research and Evaluation), which comprises 23 items and a user's manual, offers refinements of a new way to develop, report and evaluate practice guidelines.
- Key changes from the original version include a new seven-point response scale, with modifications to half of the items, and a new user's manual.
- AGREE II is available online at the AGREE Research Trust (www.agreetrust.org).

Conclusions (and food for thoughts)

- Guidelines are interesting and most probably useful
- Their writing is a difficult exercise and their implementation is a long journey (not without surprise)
- They **MUST** remain open to accommodate for local and special situations, with main emphasis on epidemiology
- At the end of the day, it will be the doctor's choice but that choice **MUST** be rational and based on best evidence applied to the patient
- Yet, societal responsibility (in this case, emergence of resistance) should not be ignored *
- Economic responsibility (best care for money) is also be important, although the acquisition costs of antibiotics are **MUCH** lower than those of many other drugs *

* not addressed in this lecture but ask questions...

Back-up slides

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	1 st line treatment	2 ^d line (and condition)
acute RTI (adult *)	<ul style="list-style-type: none"> - Acute bronchitis: an antibiotic is not indicated - Community acquired pneumonia: antibiotic (oral) if lethal risk is low (otherwise, hospitalization is required) 	<ul style="list-style-type: none"> - without co-morbidity: amoxicillin - with co-morbidity: amoxicillin-clavulanic acid <p>(if no improvement after 48 h, add a macrolide)</p>	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - amoxicillin - with co-morbidity: amoxicillin-clavulanic acid <p>(if no improvement after 48 h, replace amoxicillin by amoxicillin-clavulanic acid)</p>	<ul style="list-style-type: none"> - 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 occurrences) *
- perceived severity of the disease or disease considered as requiring antibiotic treatment	<ul style="list-style-type: none"> - 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) - dyspnoea (2) - familial epidemic (2) - certainty of a bacterial infection (1)
- fragility of the patient or whit risk	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - while waiting for the microbiological results (2) - suspicion of organism causing atypical pneumonia (1) - diagnostic uncertain and possibly worse than thought (1)

A comparative analysis of two guidelines and their rationale

Clinical situation	North American guidelines	UK guidelines
Timing of antimicrobials	Administer initial antibiotic therapy as soon as possible, after firmly establishing the presence of pneumonia	Antibiotics should be given as soon as possible and within 4 h of clinical diagnosis
Initial choice of antimicrobials	Treat all patients for pneumococcus (including DRSP) and for the possibility of atypical pathogen co-infection (if endemic rates in the community support a role for these organisms)	Treat all patients for pneumococcus. Other pathogens should be considered only in more severe cases or specific clinical situations
Initial antibiotic choice for adults hospitalized with low-moderate severity CAP treated in the community	<ul style="list-style-type: none"> selected patients with no cardiopulmonary disease or modifying factors → macrolide alone * outpatients with cardiopulmonary disease or 'modifying factors': <ul style="list-style-type: none"> monotherapy with a quinolone combination β-lactam (high dose) + macrolide or tetracycline. 	<p>Most patients can be adequately treated with oral antibiotics</p> <p>Oral therapy with amoxicillin is preferred</p> <p>When oral therapy is contraindicated, recommended parenteral choices include iv amoxicillin or benzylpenicillin, or clarithromycin</p>

* Caution: a macrolide alone should only be used in outpatients or inpatients with no risk factors for resistant *S. p.* enteric Gram-negatives or aspiration

A comparative analysis of two guidelines and their rationale

Clinical situation	North American guidelines	UK guidelines
Initial antibiotic choice for adults hospitalized with moderate severity CAP	<p>Initial IV therapy (if oral, use a quinolone [high bioavailability])</p> <p>If risk of resistant <i>S.p.</i>:</p> <ul style="list-style-type: none"> • quinolone monotherapy • or combination IV β-lactam (ceftriaxone, cefotaxime, ertapenem, ampicillin-sulbactam) + a macrolide or tetracycline. <p>→ antipseudomonal therapy only if risk factors</p>	<p>Oral therapy with β-lactam +macrolide</p> <p>If inappropriate:</p> <ul style="list-style-type: none"> • IV amoxicillin or penicillin G or IV clarithromycin, or • IV levofloxacin iv or combination iv 2^d/3^d generation cephalosporin + clarithromycin
Initial antibiotic choice for adults hospitalized with severe CAP	<p>If no pseudomonal risk factors</p> <ul style="list-style-type: none"> • β-lactam +macrolide or • antipneumococcal quinolone (gemifloxacin [oral] > moxifloxacin [oral/IV] > levofloxacin [oral/IV]) <p>Note: quinolone > macrolides if suspected or proven <i>Legionella</i> infection</p> <p>If pseudomonas risk factor</p> <ul style="list-style-type: none"> • antipseudomonal β-lactam + ciprofloxacin / high-dose levofloxacin • combination aminoglycoside + macrolide or antipneumococcal quinolone 	<p>IV β-lactamase stable β-lactam (amoxi-clav) + clarithromycin</p> <p>In penicillin-allergic patients, → 2^d/3^d generation cephalosporin + clarithromycin</p> <p>If <i>Legionella</i> is strongly suspected, consider adding levofloxacin</p>

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

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J Antimicrob Chemother 2010; **65**: 2076–2082
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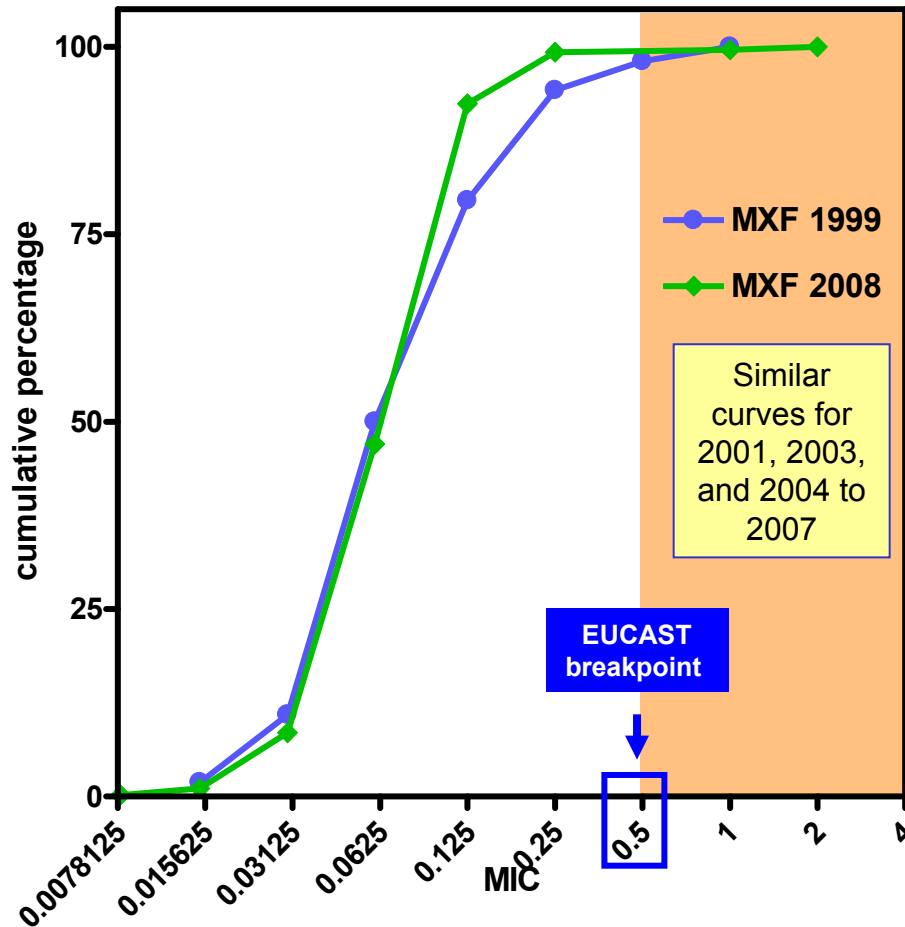
Fluoroquinolones induce the expression of *patA* and *patB*, which encode ABC efflux pumps in *Streptococcus pneumoniae*

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

S. pneumoniae susceptibility to moxifloxacin in Belgium



From data of a national collection

- Non invasive respiratory tract infections
- similar results in 2008 for a collection of *S. pneumoniae* 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.)

Is hepatotoxicity a problem for primary care physicians treating CAP ?

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

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

Andrade & Tulkens, J Antimicrob Chemother. 2011 Jul;66(7):1431-46. Epub 2011 May 17.

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

- 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**

Drug acquisition costs for treatment of CAP *

Treatment	DDD (g) ^a	DDD acquisition cost (€)		Recommended daily dose (RDD) in g ^d		RDD acquisition cost (€) ^e		Treatment duration (days) ^b		Treatment acquisition cost (€)	
		min. ^b	max. ^c	min.	max.	min.	max.	min.	max.	min. ^f	max. ^g
1 st line given alone											
amoxicillin	1	0.75	1.14	1.5	3	1.13	3.42	7	14	7.88	47.88
doxycycline	0.1	0.29	1.02	0.2/(0.1)	0.3	0.58	3.05	5	10	2.89	30.45
erythromycin	1	1.33	1.33	1	4	1.33	5.32	7	7	9.31	37.24
clarithromycin	0.5	1.05	2.85	1	1	2.09	5.69	7	10	14.63	56.90
roxithromycin	3	1.94	3.16	0.3	0.6	1.94	6.32	7	10	13.59	63.18
azithromycin	3	1.96	3.36	0.5	1.5	3.26	5.60	3	3	9.78	16.80
clindamycin	1.2	5.12	6.00	0.9	0.9	3.84	4.50	7	7	26.90	31.50
2 nd line or combinations											
co-amoxiclav	1	1.08	1.43	1.875	1.89	2.50	1.43	5	7	9.45	17.52
amoxicillin +azithromycin	1/0.3	2.71	4.50	3/0.5	3/0.5	5.51	9.02	10 / 3	10 / 5	32.28	62.20
amoxicillin +clarithromycin	1/0.5	1.80	3.99	3/1	3/1	4.34	9.11	10	10	43.40	91.10
telithromycin	0.8	3.30	3.65	0.8	0.8	3.30	3.65	7	10	23.07	36.48
levofloxacin	0.5	4.41	6.38	0.5	1	4.41	12.75	7	10	30.87	127.50
moxifloxacin	0.4	4.40	5.50	0.4	0.4	4.40	5.50	7	10	30.77	54.96

* based on guidelines (min – max) and European open pharmacy retail acquisition prices (calculator for adaptation to other prices available on request)

Carbounelle *et al.*, submitted

Guideline setting organizations with data used for this presentation

- **ERS/ESCMID**: European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases
- **AFSSAPS**: Agence Française de Sécurité Sanitaire des Produits de Santé (France)
- **ASP**: Antibiotikasenteret for primærmedisin (Norway)
- **BAPCOC**: Belgian Antibiotic Policy Coordination Committee (Belgium)
- **BTS**: British Thoracic Society (United Kingdom)
- **DSMF/SLD/SYY**: Duodecim Societas Medicorum Fennica/Suomalaisen Lääkäriseuran Duodecimin/Suomen Lastenlääkäriyhdistyksen/Suomen Yleislääketieteen Yhdistys (Finland)
- **CIO (SFN)**: Commissione Controllo Infezioni Ospedaliere (San Filippo Neri) (Italy)
- **IRF**: Institut for Rationel Farmakoterapi (Denmark)
- **KEEL**: Κέντρο Ελέγχου και Πρόληψης Νοσημάτων (Greece)
- **OEGI**: Österreichische Gesellschaft für (Austria)
- **PESC/GRS/GSI/CAPNETZ**: Paul-Ehrlich Society for Chemotherapy/German Respiratory Society/German Society for Infectiology/Competence Network Community-Acquired Pneumonia KompetenzNETZwerk (Germany)
- **RRS/IACMAC**: Russian Respiratory Society/Interregional Association of Clinical Microbiology and Antimicrobial Chemotherapy (Russia)
- **SEPAR**: Sociedad Española de Neumología y Cirugía Torácica (Spain)
- **SILF**: Svenska Infektionsläkarföreningen (Sweden)
- **SIGN**: Scottish Intercollegiate Guidelines Network (Scotland)
- **SPILF**: Société de Pathologie Infectieuse de Langue Française (France and other French-speaking countries)
- **SPP**: Sociedade Portuguesa de Pneumologia (Portugal)
- **SSI**: Swiss Society for Infectious Diseases (Switzerland)
- **SWAB**: Stichting Werkgroep AntibioticaBeleid (The Netherlands)
- **CIDS/CTS**: Canadian Infectious Disease Society/Canadian Thoracic Society (Canada)
- **IDSA/ATS**: American Thoracic Society Infectious Diseases Society of America (United States of America)
- **ALAT**: Asociación Latinoamericana del Tórax (Latin America)
- **BTA**: Brazilian Thoracic Association (Brazil)
- **SACAPWG**: Saudi Arabian Community Acquired Pneumonia Working Group (Saudi Arabia)
- **SATS**: South African Thoracic Society