Guidelines in Community-Acquired Pneumonia (CAP) and Chronic Obstructive Lung Disease (COPD): from diversity to logics

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Disclosures

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- *Université catholique de Louvain* for personal support
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  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics…
- Other relationships in relation to this talk
  - Belgian Antibiotic Policy Coordination Committee,
  - Belgian Transparency and Reimbursement Committees
  - Participation to EMA expert meetings for novel antibiotics and as Industry supporting expert for assessment of toxicity of older ones

Do we have a problem ?

Obituary

J.-M. Ghuysen

This man discovered the mode of action of penicillins

Ann. Rev. Biochem. 1979. 48:73–101

USE OF MODEL ENZYMES IN THE DETERMINATION OF THE MODE OF ACTION OF PENICILLINS AND Δ^3-CEPHALOSPORINS[1]

Jean-Marie Ghuysen, Jean-Marie Frère, Mélina Leyh-Bouille, Jacques Coyette, Jean Dusart, and Martine Nguyen-Distèche

Service de Microbiologie, Faculté de Médecine, Institut de Botanique, Université de Liège, 4000 Sart Tilman, Liège, Belgium

and died from invasive pneumococcal infection …

http://www.cip.ulg.ac.be/newsite/pdf/jmghuysen.pdf

Do we have a problem ?

- CAP:
  - remains a major acute cause of death (3^{d} to 7th);
  - *Streptococcus pneumoniae* is the most commonly identified pathogen, but other bacteria may be critical in specific environments (the causative organisms remains, however, unidentified in 30% to 50% of cases).
- COPD
  - also a major cause of death (4th in 2006 and projected 3d in 2020)
  - runs as often undiagnosed at early stages
  - "progresses" to decreases of respiratory function by successive infectious exacerbations

What is my goal ?

- Discuss with you one way to try improving the treatment of CAP and COPD

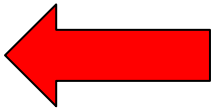
What this lecture will be about?

- Why guidelines?
- Are guidelines unanimous on defined topics?
- What is the quality of guidelines?
- What could be their limitations in daily clinical practice ?
- Practical CAP guidelines
- Practical COPD guidelines
- Towards a conclusion and actions …

the case of the CAP guidelines

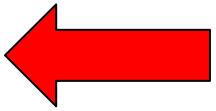
Guidelines: origin, basis and use

- Clinical guidelines aim at **guiding decisions and criteria** regarding diagnosis, management, and treatment

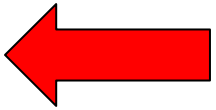


- Guidelines have been used since the beginning of medicine

- 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 about 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

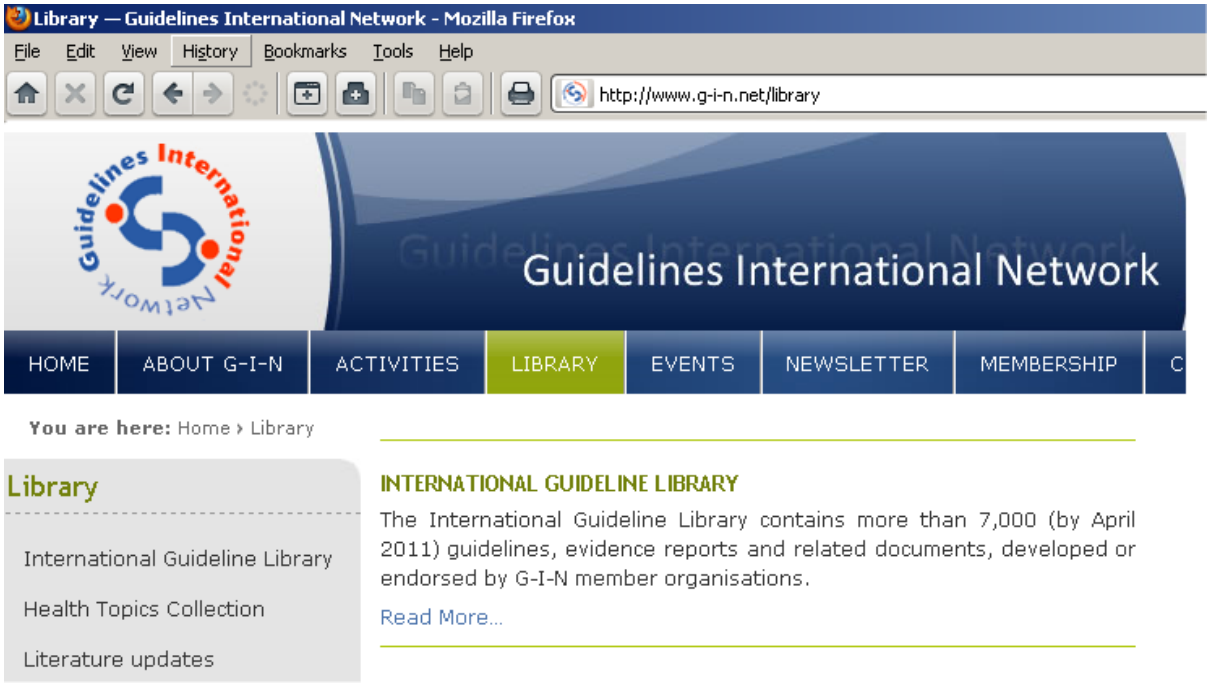
- But guidelines are also often seen as a mean to **standardize medical care** with 2 potential consequences/goals:

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

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

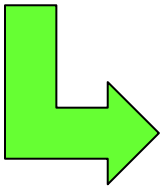
Guidelines: who and where?

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



How to judge guidelines ?

- Guidelines should take enough parameters into account (qualitatively and quantitatively) to be pertinent
- Guidelines must linked to 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 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 instrument

- Originally developed through a grant from the European Union
- Published in its version 1 in 2001
- Updated as version 2 in 2010

http://www.agreetrust.org/

The 6 main domains

AGREE II INSTRUMENT

I. Domain 1. Scope and Purpose

II. Domain 2. Stakeholder Involvement

III. Domain 3. Rigour of Development

IV. Domain 4. Clarity of Presentation

V. Domain 5. Applicability

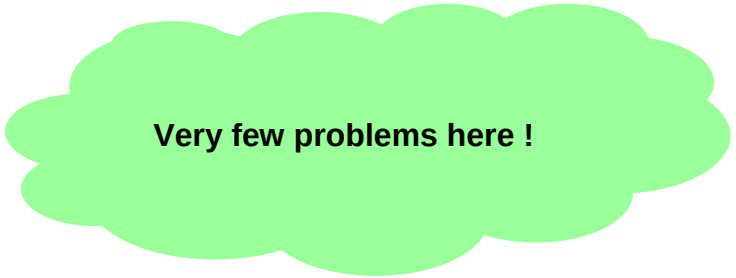
VI. Domain 6. Editorial Independence

***A**ppraisal of **G**uidelines **R**esearch and **E**valuation – developed through an EU-funded research project and available on http://www.agreetrust.org/

Looking at the main subdomains

I. Scope and purpose

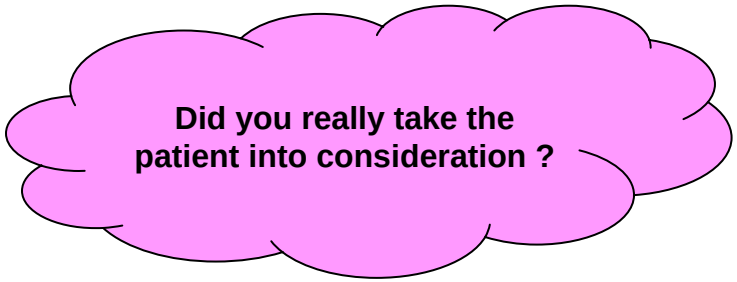
1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.



Looking at the main critical subdomains

II. Stakeholder involvement

1. **The guideline development group includes individuals from all relevant professional groups.**
2. **The views and preferences of the target population (patients, public, etc.) have been sought.**
3. The target users of the guideline are clearly defined.



Looking at the main critical subdomains

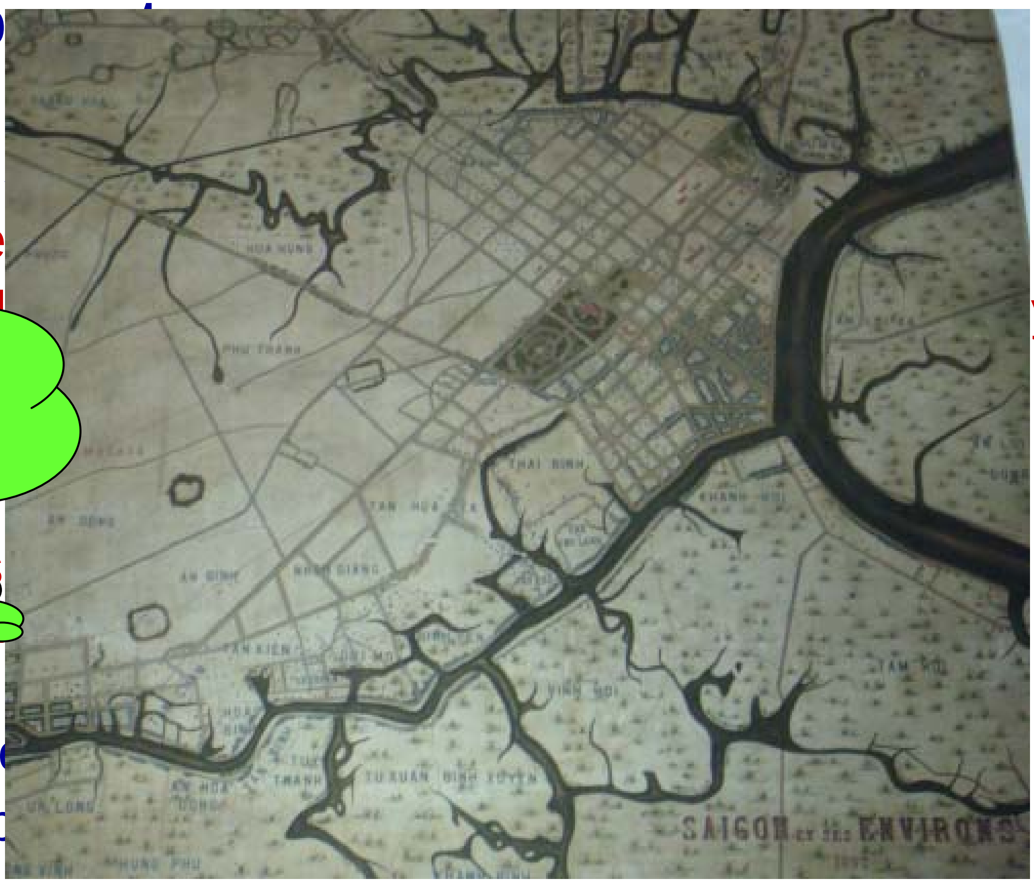
III. Rigour of development

1. Systematic methods were used to search for evidence.
2. The criteria for selecting the evidence are clearly described.
3. The strengths and limitations of the body of evidence are clearly described.
4. The methods for formulating the recommendations are clearly described.
5. The health benefits, side effects, and risks have been considered in formulating the recommendations.
6. There is an explicit link between the recommendations and the supporting evidence.
7. The guideline has been externally reviewed by experts prior to its publication.
8. **A procedure for updating the guideline is provided.**

Perhaps a most critical point…

Looking at the main critical subdomains

III. Rigour of develop



1. Systematic method
2. The criteria for sele

using this map may not be the best way to walk in Ho Chi Minh !!

5. ... benefits ... considered in form
6. There is an explicit ... supporting evidence
7. The guideline has b... its publication.
8. **A procedure for updating the guideline is provided.**

Perhaps a most critical point…

Looking at the main critical subdomains

V. Applicability

1. **The guideline describes facilitators and barriers to its application.**
2. The guideline provides advice and/or tools on how the recommendations can be put into practice.
3. **The potential resource implications of applying the recommendations have been considered.**
4. **The guideline presents monitoring and/or auditing criteria.**

How real is this in your guidelines ?

Looking at the main critical subdomains

V. Applicability

1. **The guideline**
   application.
2. The guideline p
   recommendatio
3. **The potential**
   i
4. **resents monitoring and/or auditing criteria.**

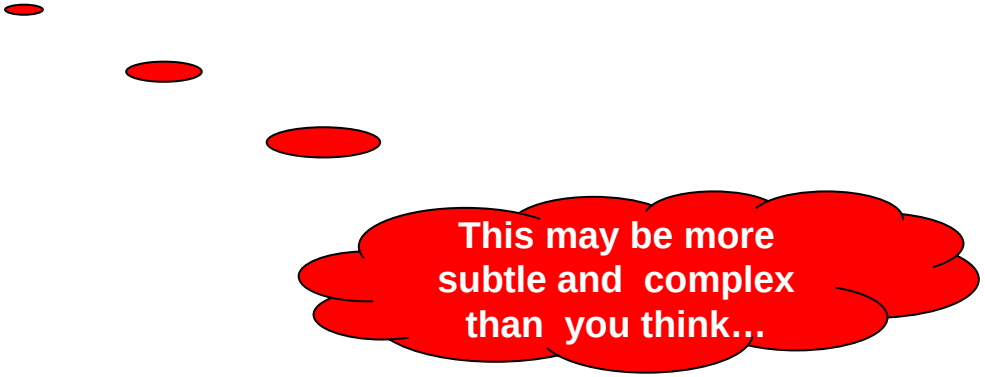
Can you find easily which connection is faulty ?

How real is this in your guidelines ?

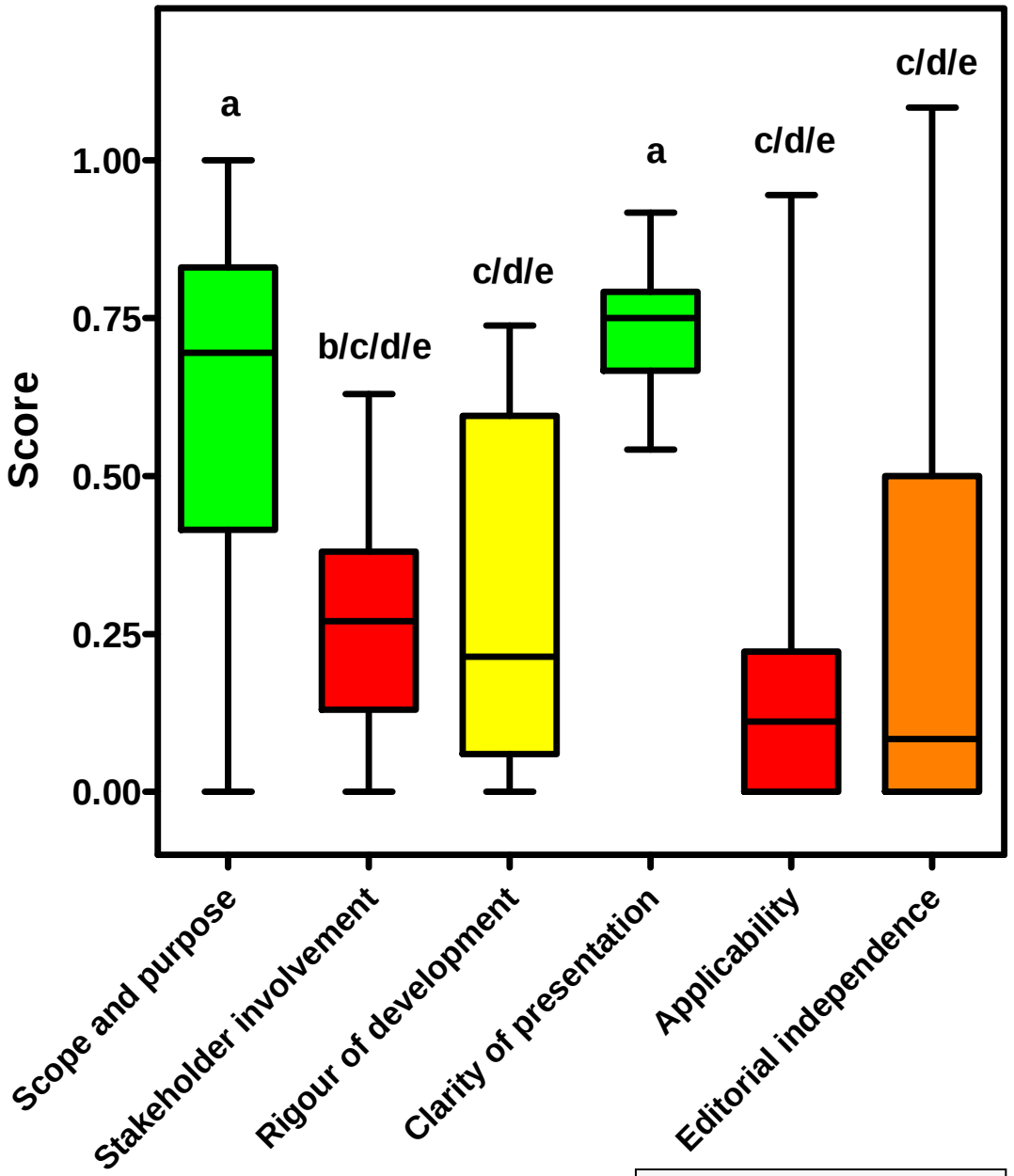
Looking at the main critical subdomains

VI. Editorial Independence

1. **The views of the funding body have not influenced the content of the guideline.**
2. **Competing interests of guideline development group members have been recorded and addressed.**



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.*, in preparation

Guidelines: are they used?

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

Example 1: family practice

BMC Family Practice

BioMed Central

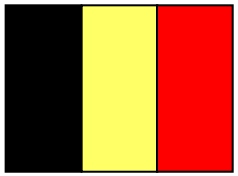
Research article

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



Using Belgian data so as not to criticize anyone but our-selves

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.

Heselmans A, et al. BMC Fam Pract 2009;10:64.

Guidelines: are they used?

Example 2: hospital practice

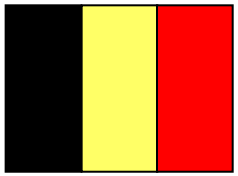
Journal of Antimicrobial Chemotherapy (2008) **62**, 189–195
doi:10.1093/jac/dkn143
Advance Access publication 8 April 2008

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



Using Belgian data so as not to criticize anyone but our-selves

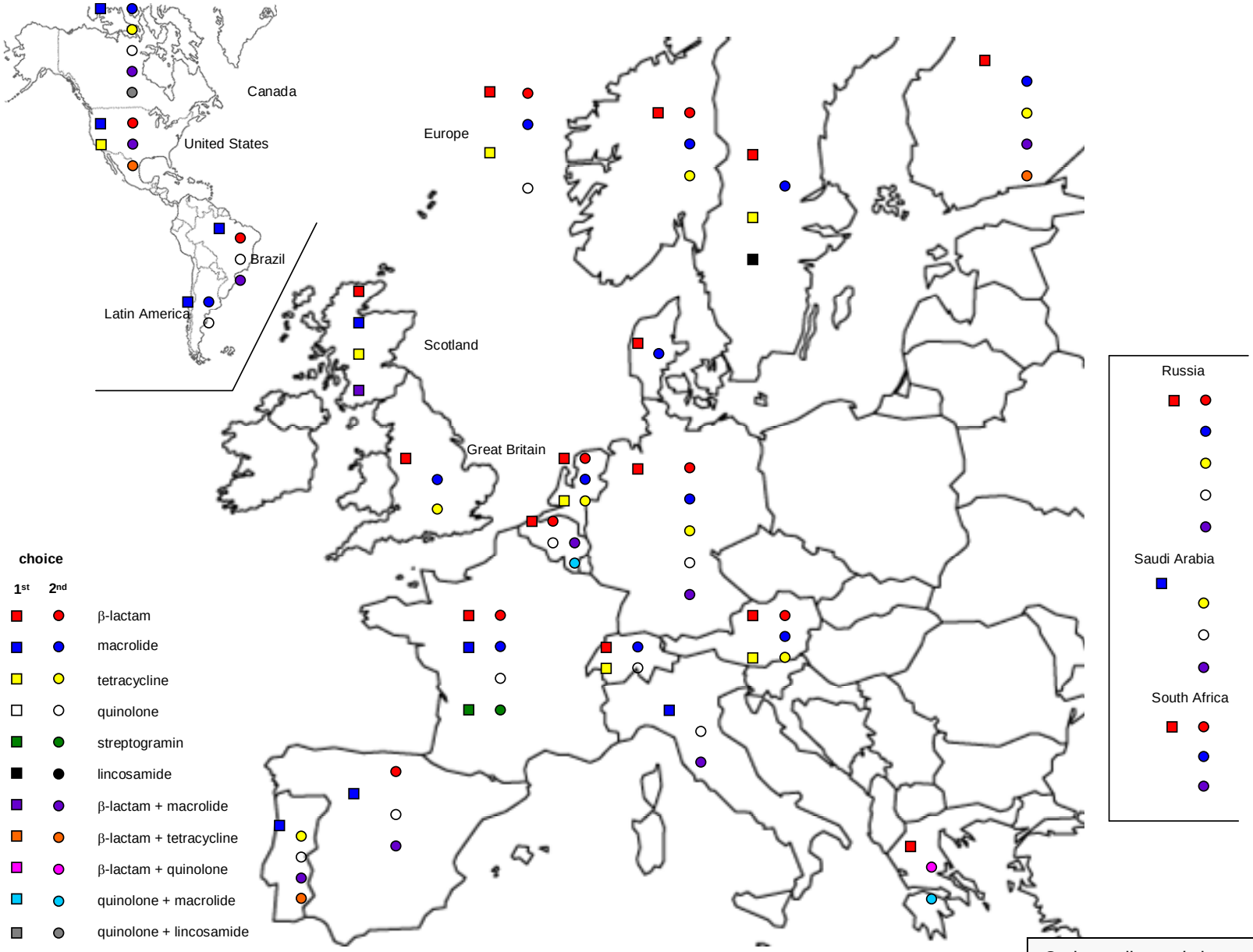
Conclusions: **Locally developed hospital guidelines experience the same barriers as other guidelines. Within one hospital, prescribers have to be seen as a number of different target groups instead of a homogeneous population. For an optimal effect, interventions will have to consider these differences. 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.**

Cortoos PJ, et al. J Antimicrob Chemother 2008;62(1):189-95.

Guidelines: are they homogenous?

- They need not be, 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 may be anticipated from the above considerations…

CAP guidelines: many variations



Carbonnelle *et al.*, in preparation

A (short)* summary of variations in Europe… (moderate CAP; empiric)

+ = 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[1] Europe	**+** (+)	(+)	**+**	(+)			
AFSSAPS[2] France	**+** (+)	**+** (+)		(+)	**+** (+)		
BTS[3] Great Britain	**+**	(+)	(+)				
PESC[4] Germany	**+** (+)	(+)	(+)	(+)		(+)	
SEPAR[5] Spain	(+)	**+**		(+)		(+)	
SPP[6] Portugal		**+**	(+)	(+)		(+)	(+)

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

[a] see back-up slides for definition of acronyms

[b] amoxicillin most often cited

[c] levofloxacine or moxifloxacin

[d] pristinamycin

1. http://www.escmid.org/fileadmin/src/media/PDFs/2News_Discussions/2Position_Papers/ICM_Article_HAP_v35_2009.pdf
2. http://www.em-consulte.com/showarticlefile/143561/pdf_51690.pdf
3. http://www.thepcrj.org/journ/vol19/19_1_21_27.pdf
4. http://media.econtext.de/v1/stream/16-236/acbdd299911a2e9c099c465d9d011062/1274968644/16/236.econtext
5. http://www.archbronconeumol.org/bronco/ctl_servlet?_f=40&ident=13075322
6. http://www.sppneumologia.pt/sites/sppneumologia.pt/files/pdfs/RPP_2005_3_243_Praticas.pdf
7. http://cid.oxfordjournals.org/content/44/Supplement_2/S27.full.pdf
8. http://www.archbronconeumol.org/bronco_eng/ctl_servlet?_f=40&ident=13065051
9. http://www.jornaldepneumologia.com.br/english/artigo_detalhes.asp?id=1401

A comparison of two CAP guidelines separated by an ocean …

Clinical situation	North American guidelines	UK guidelines
Initial antibiotic choice for adults hospitalized with low-moderate severity CAP treated in the commu	• selected patients with no cardiopulmonary disease or modifying factors → **macrolide alone *** • outpatients with cardiopulmonary disease or 'modifying factors': – monotherapy with a **quinolone** – combination **β-lactam (high dose) + macrolide or tetracycline.**	Most patients can be adequately treated with oral antibiotics **Oral therapy with amoxicillin is preferred** When oral therapy is contraindicated, recommended parenteral choices include **iv amoxicillin or benzylpenicillin, or clarithromycin**
Initial antibiotic choice for adults hospitalized with severe CAP	If no pseudomonal risk factors • **β-lactam +macrolide** or • **antipneumococcal quinolone** (gemifloxacin [oral] > moxifloxacin [oral/IV] > levofloxacin [oral/IV]) Note: quinolone > macrolides if suspected or proven *Legionella* infection If pseudomonas risk factor • **antipseudomonal β-lactam + ciprofloxacin / high-dose levofloxacin** • combination **aminoglycoside + macrolide or antipneumococcal quinolone**	**IV β-lactamase stable β-lactam (amoxi-clav) + clarithromycin** In penicillin-allergic patients, → 2^{d}/3^{d} generation cephalosporin + clarithromycin If *Legionella* is strongly suspected, consider adding levofloxacin

Adapted from NM.S. Niederman Community-acquired pneumonia. *In* Infectious Diseases (3d edition; J. Cohen, W. Powderly & S. Opal, eds), chap. 27 Elsevier/Mosby, 2010 (ISBN 978-0-323-04579-7). Available on line at http://www.expertconsult.com

What about COPD guidelines ?

American Thoracic Society

EUROPEAN RESPIRATORY SOCIETY

Standards for the Diagnosis and Management of Patients with COPD

2004

NHS National Institute for Health and Clinical Excellence

CG101 Chronic obstructive pulmonary disease (CG101)

2010

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE™

2013

- http://www.thoracic.org/clinical/copd-guidelines/resources/copddoc.pdf
- http://guidance.nice.org.uk/CG101/Guidance/pdf/English
- http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf

Comparing guidelines for antibiotics in COPD

ATS / ERS 2004

- Exacerbations are a common cause of morbidity and mortality
- Antibiotics may be initiated in patients with change in sputum characteristics (purulence and/or volume)
- Choice should be based on local bacteria resistance patterns with (by order) amoxicillin/clavulanate, respiratory fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin), and, if *Pseudomonas* spp. and/or other *Enterobactereaces* spp. are suspected, combination therapy

BTS / NICE 2010

- meta-analysis of 9 trials found a small but statistically significant effect favouring antibiotics over placebo
- Type 1 (Anthonisen's) exacerbations (increased amount and purulence of sputum and dyspnoea) benefited the most with resolution of symptoms
- Patients who used antibiotics experienced lower odds for all-cause 30-day mortality
- macrolides had the lowest relative odds for mortality (OR 0.58, 95% CI 0.47 to 0.73) and fluoroquinolones had the highest relative odds (OR 0.98, 95% CI 0.84 to 1.15) *.

* Canadian study published in 2000 (fluoroquinolones were mainly ciprofloxacin and ofloxacin that have low activity against *S. pneumoniae* [intermediate in EUCAST])

GOLD 2013

- The goals are to minimize the impact of the current exacerbation … with pharmacologic therapies including bronchodilators, corticosteroids, and antibiotics
- the use of antibiotics in exacerbations remains controversial… but a systematic review has shown that antibiotics reduce the risk of short-term mortality by 77%
- The choice of the antibiotic should be based on the local bacterial resistance pattern..

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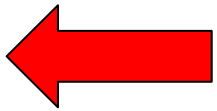
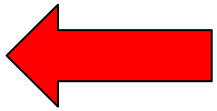
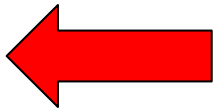
Key questions to ask when setting guidelines in infectious diseases (with application to CAP/COPD)

- How sure are you of the diagnosis?
- **Which are the main pathogens and their current resistance patterns?**
- How should the therapy be initiated (empiric *vs.* directed)
- **Which level of adverse effects is acceptable?**
- **Which patients do you mainly treat?**
- Does cost matter?
- What are your real choices?



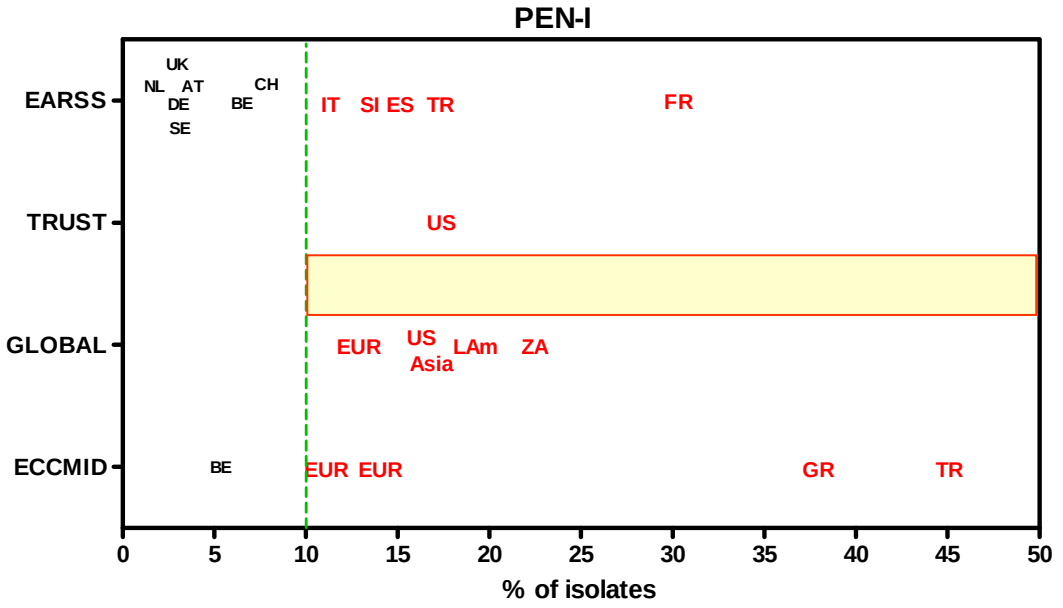


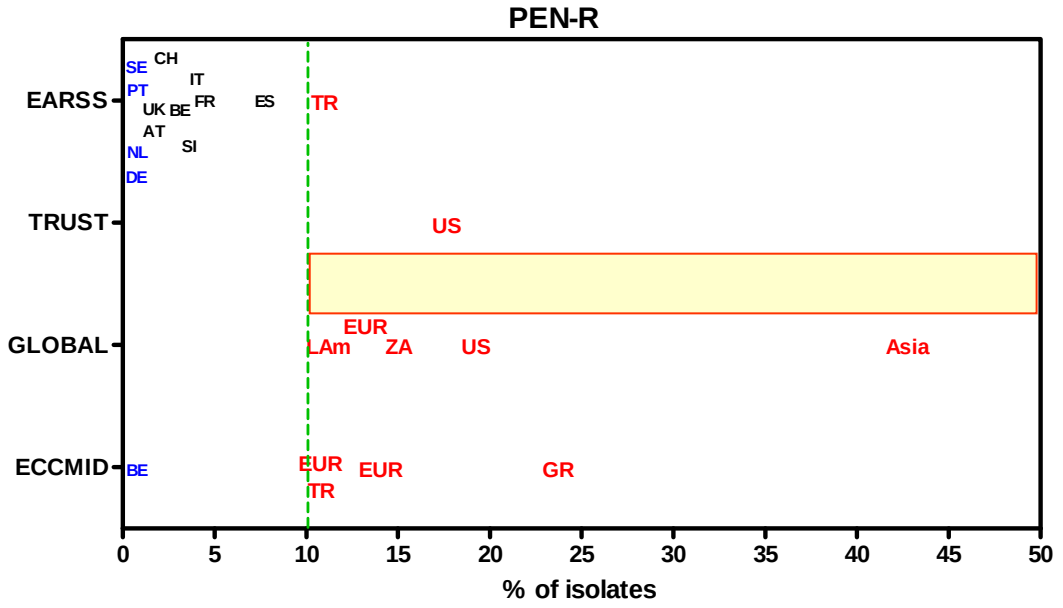


Resistance of *S. pneumoniae* *

*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

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- **Riedel:** Eur J Clin Microbiol Infect Dis. 2007 Jul;26(7):485-90.
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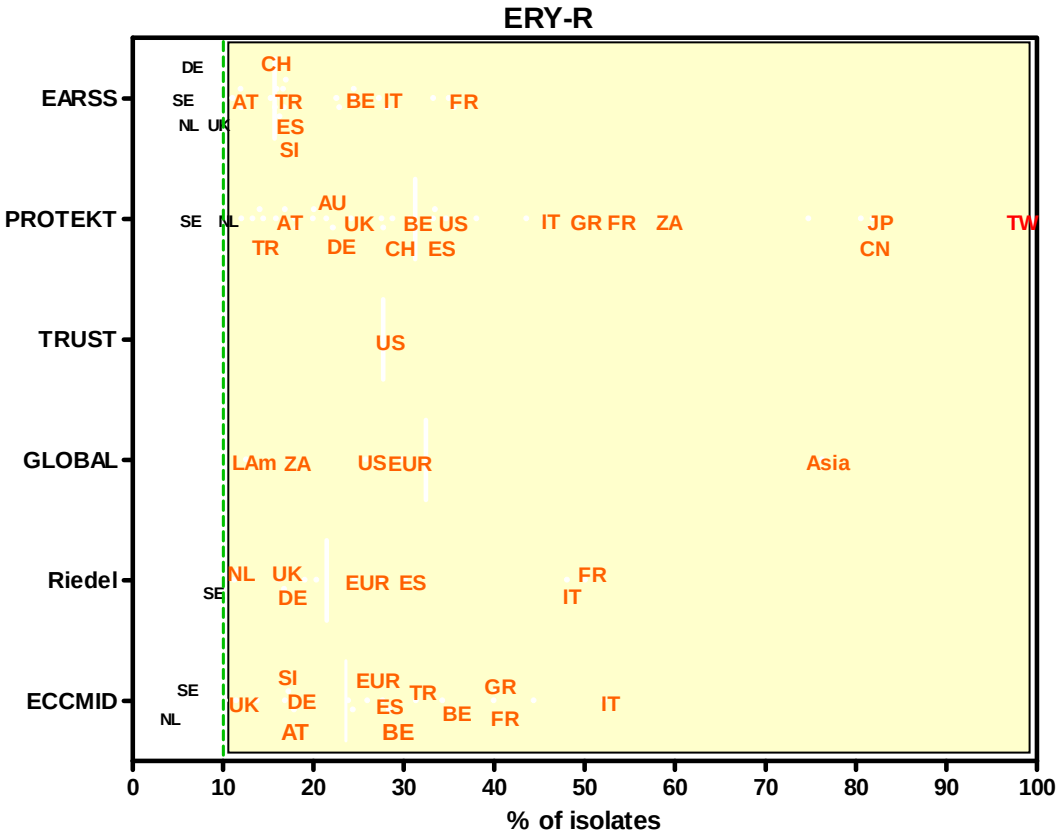
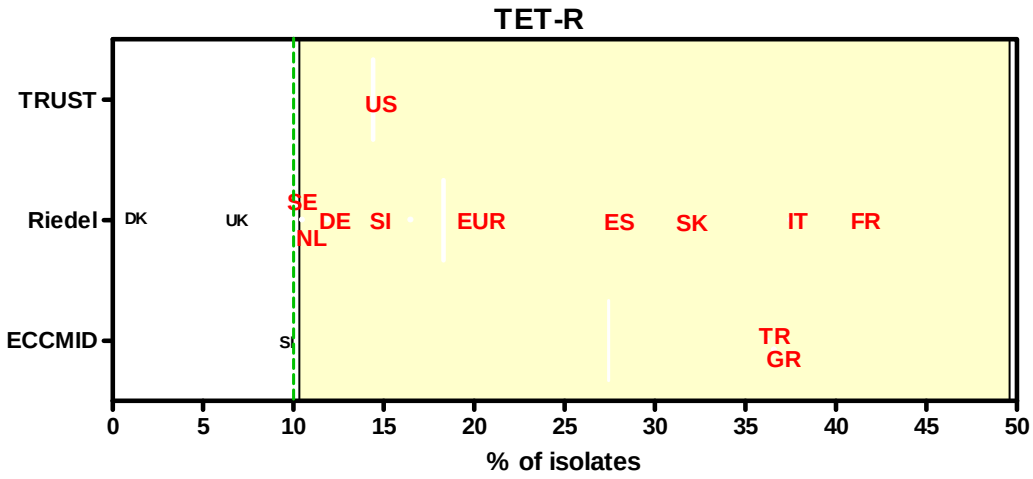
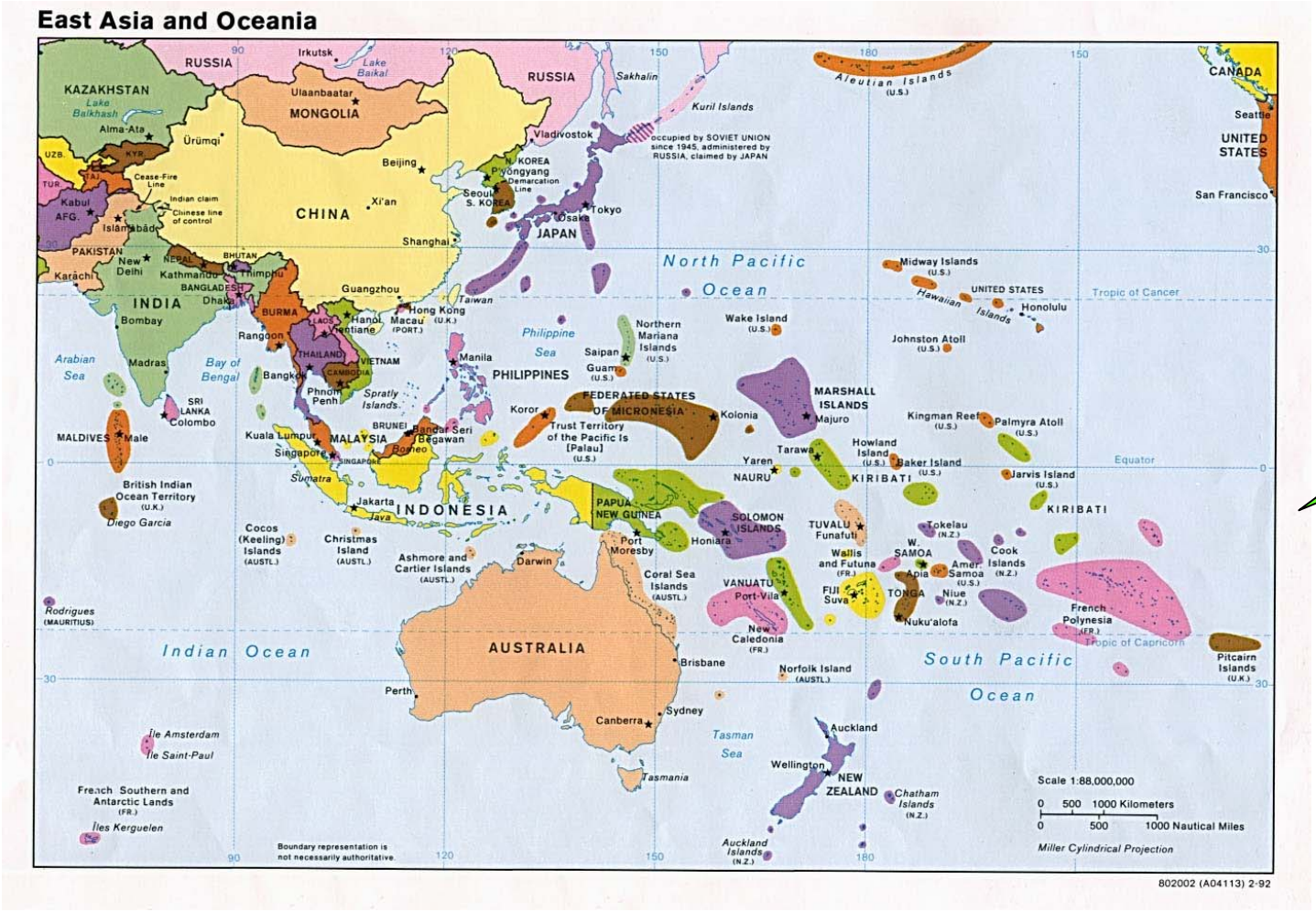




The message: make and use surveillance studies

Countries should know THEIR resistance patterns !



But what about breakpoints ?

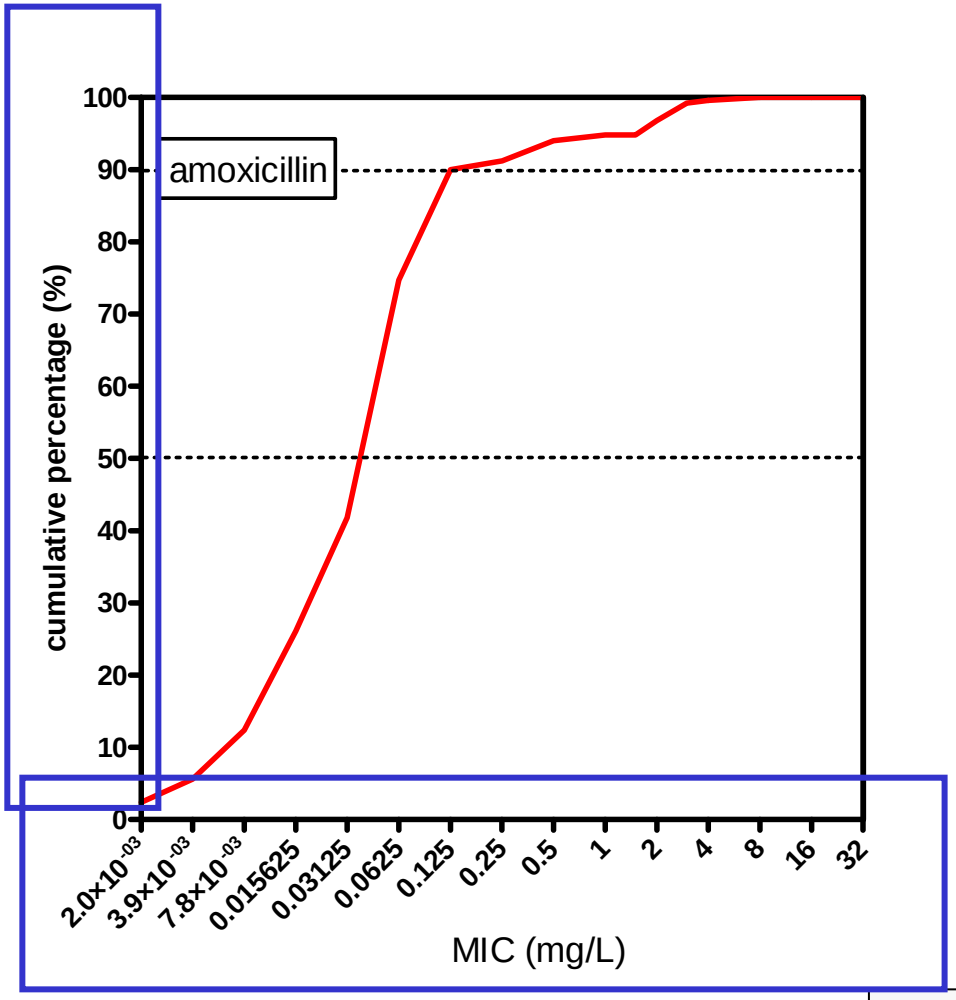
Do we need breakpoints ? To be honest, I always wondered ...

But what about breakpoints ?

Vérité en-deçà des Pyrénées,
erreur au-delà…

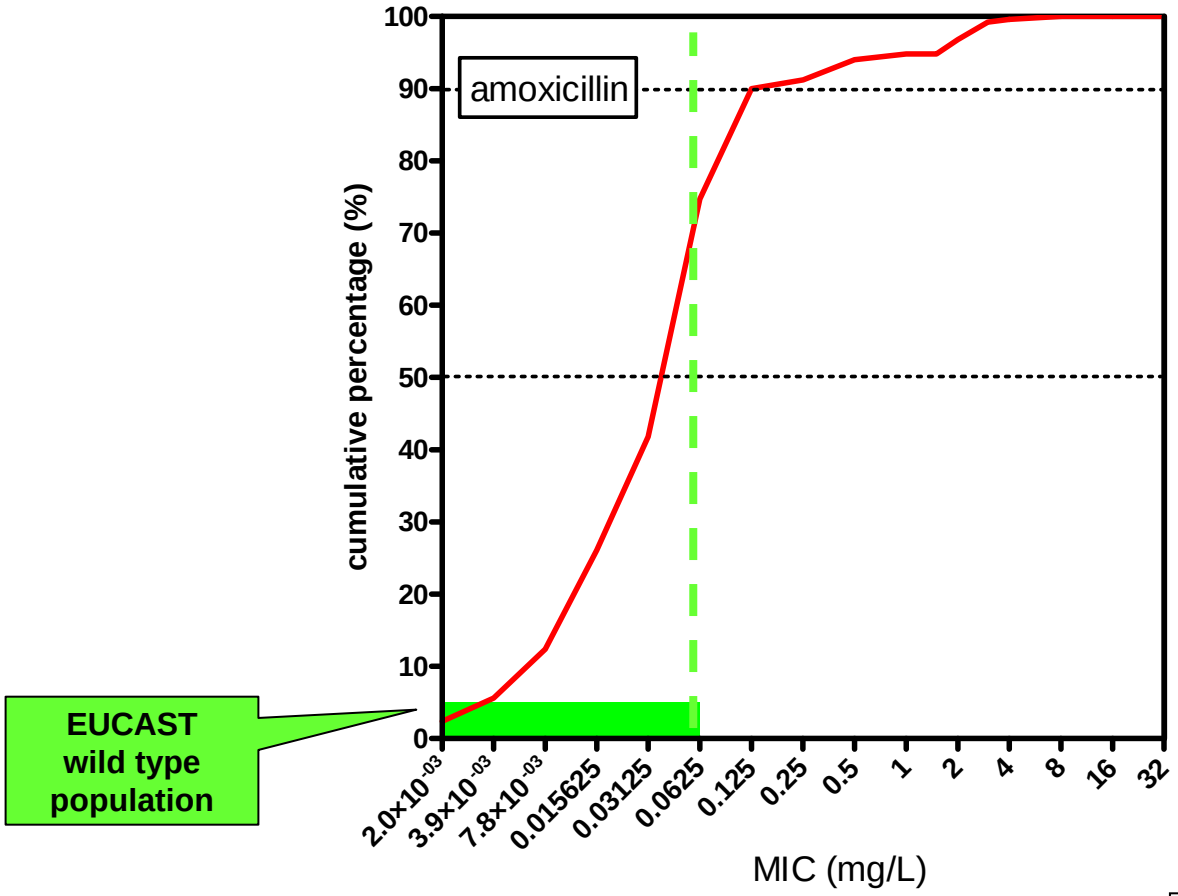
The frontispiece of Geert Hofstede's influential book, *Culture's consequences: Comparing values, behaviors, institutions, and organizations across nations* (Hofstede, 2001) includes the following quote: "Vérité en-deça des pyrénées, erreur au-delà". Written about 350 years ago by the French mathematician and physicist Blaise Pascal and included in his *Pensées*, Hofstede's translation is "There are truths on this side of the Pyrenees that are falsehoods on the other."

MICs is a continuous variable…



Belgian data:
Lismond et al. Int. J. Antimicrob Agents. 2012 Mar;39(3):208-16.

MICs is a continuous variable…
on which you can add information…



Belgian data:
Lismond et al. Int. J. Antimicrob Agents. 2012 Mar;39(3):208-16.

MICs is a continuous variable…
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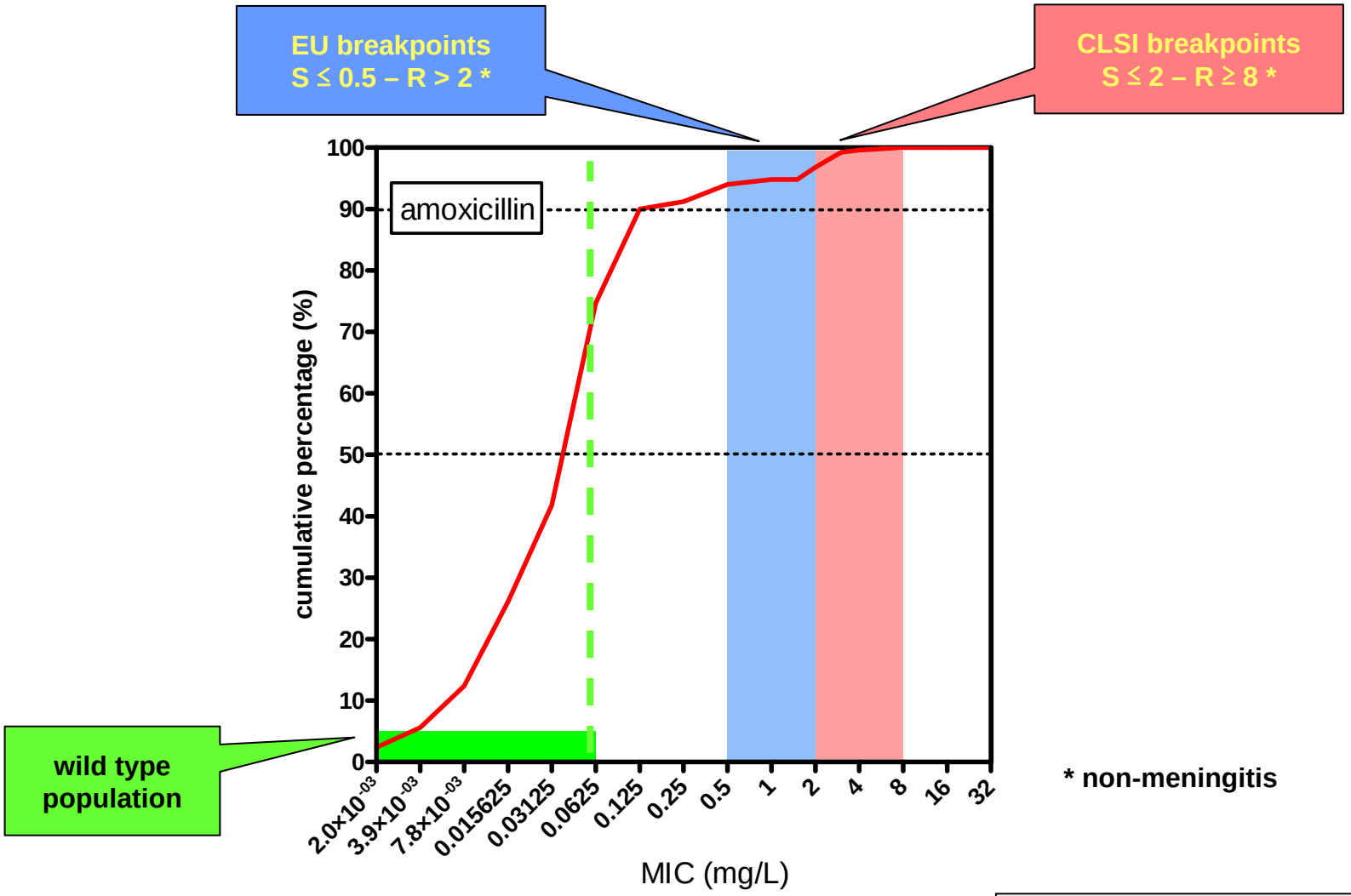


Belgian data:
Lismond et al. Int. J. Antimicrob Agents. 2012 Mar;39(3):208-16.

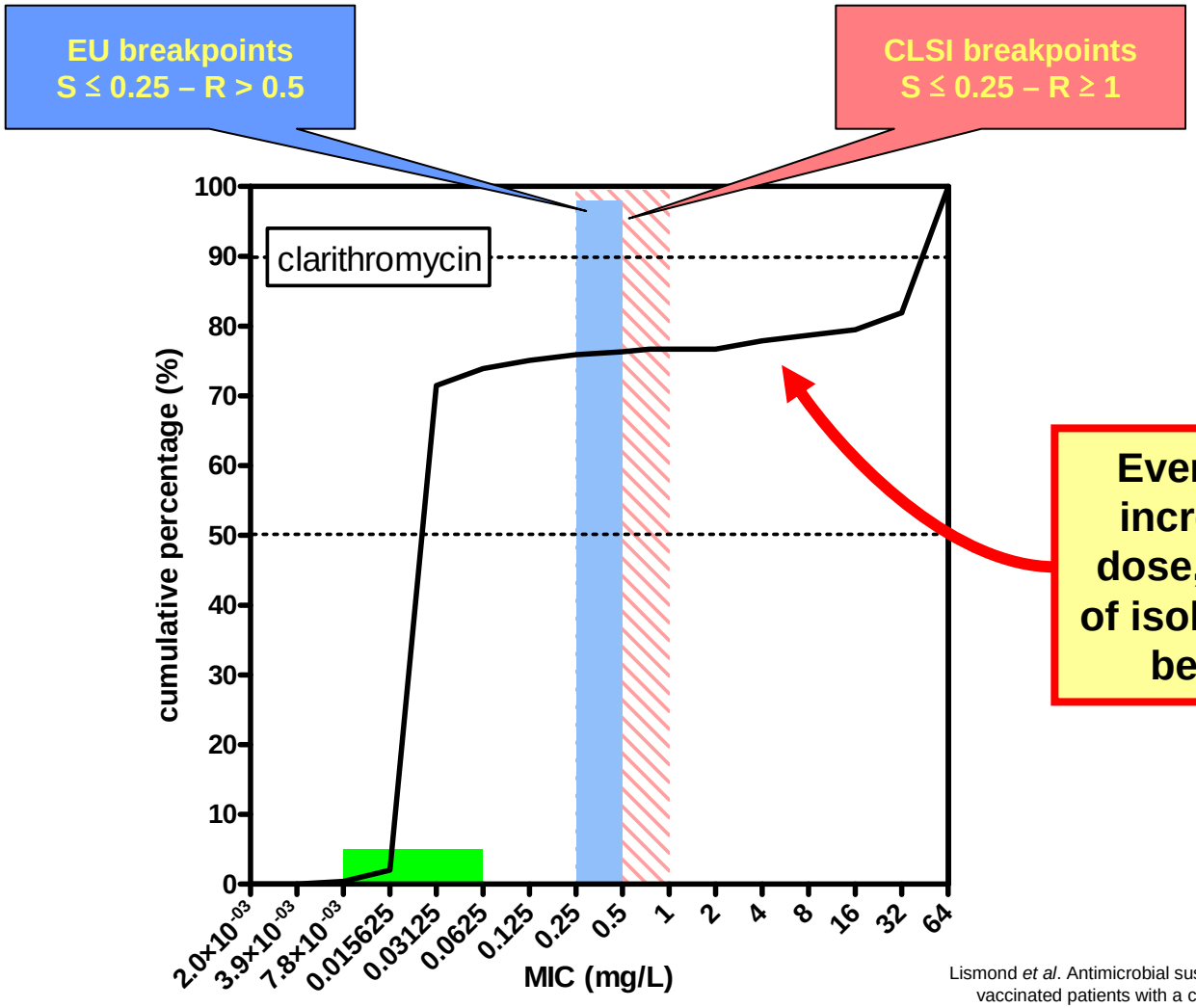
Warning about breakpoints (EUCAST *vs.* CLSI) for *S. pneumoniae* (non meningitis)

- With the new CLSI breakpoint (MIC ≥ 8 mg/L), very few isolates will be defined as resistant….
- In fact, most experts believe that CAP caused by organisms with a penicillin MIC of 4 mg/L or higher (still an uncommon finding), can lead to an increased risk of death.[1]
- For that reason, Europe has maintained its R breakpoint at > 2 mg/L.[2]
- **Dosage adaptation over the original 250 mg BID is necessary for isolates with MIC > 0.125**
  ➔ 0.5 g TID, 1 g TID, …

1. Feikin DR, et al. Am J Public Health 2000;90(2):223-9.
2. EUCAST clinical breakpoints (http://www.eucast.org)

But what about macrolides ?

Susceptibility profile of *S. pneumoniae* to clarithromycin in Belgium



Even if you try increasing the dose, up to 25 % of isolates will not be covered

Lismond *et al*. Antimicrobial susceptibility of Streptococcus pneumoniae isolates from vaccinated and non-vaccinated patients with a clinically confirmed diagnosis of community-acquired pneumonia in Belgium. Int J Antimicrob Agents. 2012 Mar;39(3):208-16.

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

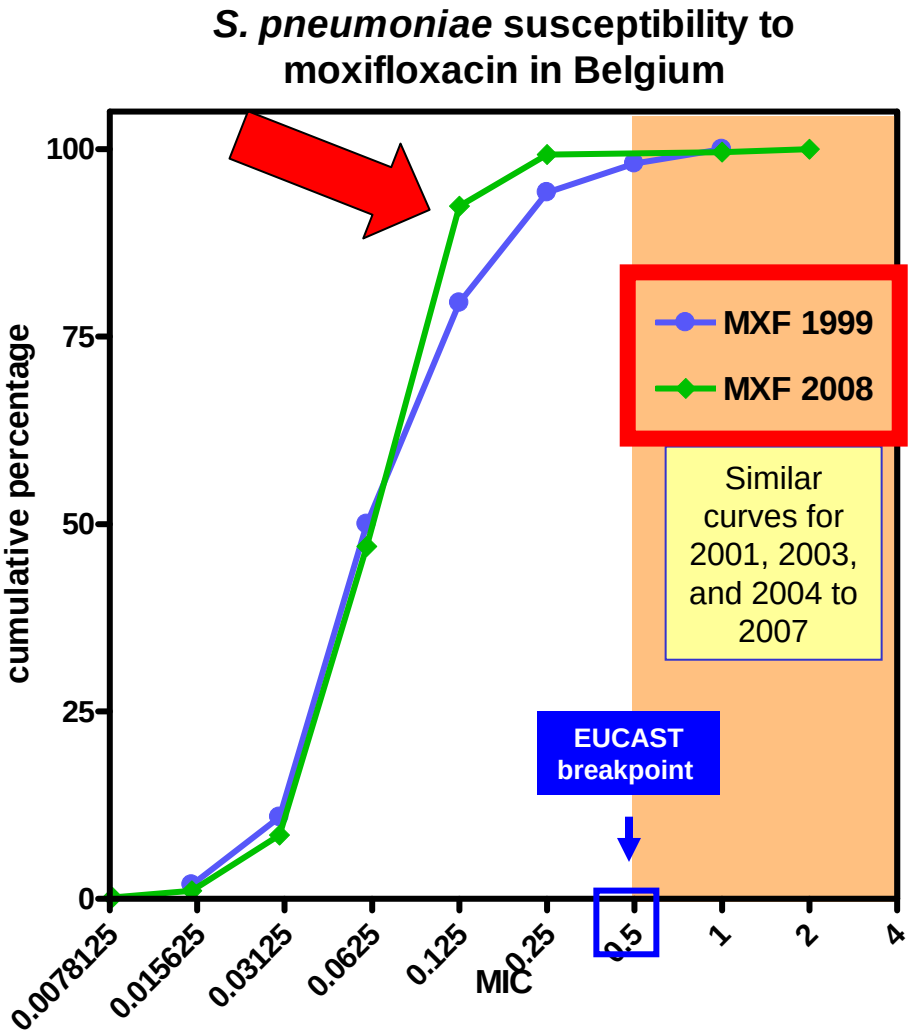
Fluoroquinolones induce the expression of *patA* and *patB*, which encode ABC efflux pumps in *Streptococcus pneumoniae*

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*

Avrain L, et al. J Antimicrob Chemother 2007;60(5):965-72.
El Garch F, et al. J Antimicrob Chemother 2010;65(10):2076-82.

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



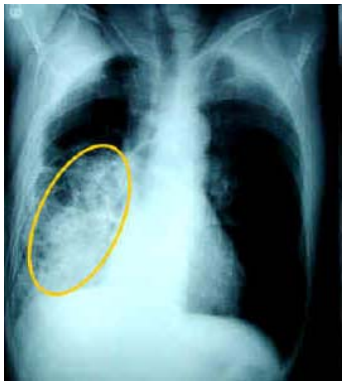
From data of a <u>national</u> collection

- 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)
- Data available yearly for 1999 through 2008
- http://www.iph.fgov.be

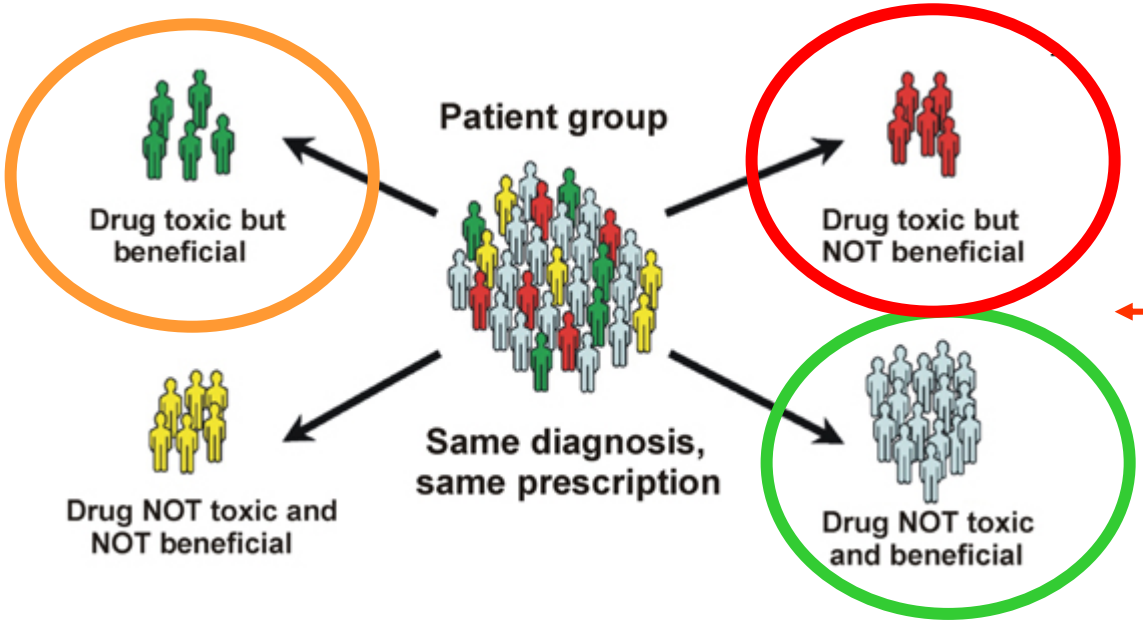
Vanhoof RLM, et al. 19th European Congress of Clinical Microbiology and Infectious Diseases. May, 16-19 2009, Helsinki.

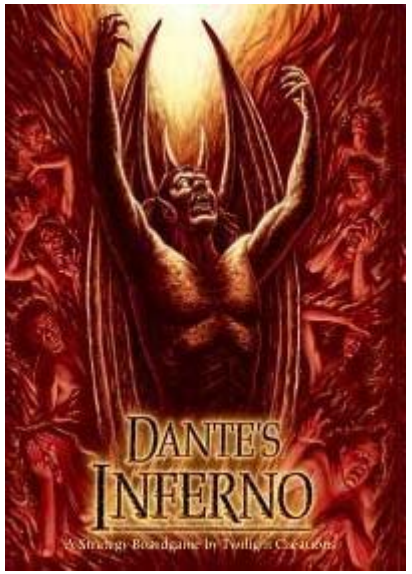
And what about side effects…



therapy ?

side effects ?





All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
β-lactams	**amoxicillin**	• **Anaphylactic reactions** • *Clostridium difficile*-associated colitis • Digestive tract: diarrhoea, nausea • CNS: agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness.
	amoxicillin – clavulanic acid	• **Anaphylactic reactions** • *Clostridium difficile*-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	• **Anaphylactic reactions and cutaneous eruptions** • Nephrotoxicity (aggrav. with loop diuretics) • Hepatic toxicity • *Clostridium difficile*-associated colitis
	ceftriaxone	• **Anaphylactic reactions and cutaneous eruptions** • Digestive tract:diarrhoea, nausea • *Clostridium difficile*-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**	• Anaphylactic reactions • *Clostridium difficile*-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	• Anaphylactic reactions • *Clostridium difficile*-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	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • **Hepatotoxicity** • Visual disturbance • Loss of consciousness • Respiratory failure in patients with myastenia gravis • **QTc prolongation** • **Drug interactions (CYP450)** • Digestive tract: diarrhoea, nausea, vomiting, dysgueusia • CNS: headache, dizziness

* 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
fluoroquinolones	levofloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-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	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-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 so far:

- 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**

Do not say that …

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

An example of much "talked about toxicity": hepatotoxicity

Ciprofloxacin Levofloxacin Moxifloxacin	Tetracycline	Erythromycin Clarithromycin Penicillins	Co-trimoxazole Amoxicillin/ clavulanate	Telithromycin Trovafloxacin
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: incidence as a percentage of prescriptions for antibiotics with main indications for use in the community setting

Andrade RJ, Tulkens PM. J Antimicrob Chemother 2011;66(7):1431-46.

The 3 major "points for attention" in guidelines

Are they regularly updated and modernized ?

Are they not too dogmatic ?

Can they really be used for most patients ?

Conclusions (and food for thought)

- Guidelines are interesting and most probably useful
- Their writing is a difficult exercise and their implementation is a long journey (unsurprisingly)
- They MUST remain open to accommodate for local and special situations, with the primary 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
- Societal responsibility (in this case, the emergence of resistance) should not be ignored*
- Economic responsibility is also important, although the acquisition costs of antibiotics are MUCH lower than those of many other drugs*

***Not addressed in this lecture but do ask questions…**

Back-up slides

A comparison of two guidelines separated by an ocean

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	• selected patients with no cardiopulmonary disease or modifying factors → **macrolide alone *** • outpatients with cardiopulmonary disease or 'modifying factors': – monotherapy with a **quinolone** – combination **β-lactam (high dose) + macrolide or tetracycline.**	Most patients can be adequately treated with oral antibiotics **Oral therapy with amoxicillin is preferred** When oral therapy is contraindicated, recommended parenteral choices include **iv amoxicillin or benzylpenicillin, or clarithromycin**

* 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

Adapted from NM.S. Niederman Community-acquired pneumonia. *In* Infectious Diseases (3d edition; J. Cohen, W. Powderly & S. Opal, eds), chap. 27 Elsevier/Mosby, 2010 (ISBN 978-0-323-04579-7). Available on line at http://www.expertconsult.com

Main pathogens: a more realistic view

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

Adapted from NM.S. Niederman Community-acquired pneumonia. *In* Infectious Diseases (3d edition; J. Cohen, W. Powderly & S. Opal, eds), chap. 27 Elsevier/Mosby, 2010 (ISBN 978-0-323-04579-7). Available on line at http://www.expertconsult.com

Which resistance?

Organisms	Antibiotic class	Main mechanism	Clinical consequence
S. pneumoniae	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, fluoroquinolones	efflux (*mefA*)	**intermediate (but …)**
		target alteration (*ermB*)	**full resistance**
***H. influenzae* ***	β-lactams	β-lactamase	full resistance **(reversed by clavul. acid)**
		alteration of PBPs	increase in MIC (clinically rare)
Mycoplasma, Chlamydia, Legionella* *	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

Information from:

- D.M. Musher. *Streptooccus pneumoniae. In*: Principles and Practice of Infectious Diseases, 7th Ed. Mandell et al. eds. chapter 200, Elsevier;available on line at http://www.expertconsult.com
- NM.S. Niederman Community-acquired pneumonia. *In* Infectious Diseases (3d edition; J. Cohen, W. Powderly & S. Opal, eds), chap. 27 Elsevier/Mosby, 2010 (ISBN 978-0-323-04579-7). Available on line at http://www.expertconsult.com
- and other original publications (in PubMed)

Limitations in daily practice: an example from general practice

- 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**

Feron *et al.* Pathologie Biologie (Paris) (2009) 57:61-64, and Feron *et al.* in preparation

Limitations in daily practice: an example from general practice

- **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) - 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)

Feron *et al*. 18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)Barcelona, Spain, 19-22 April 2008
Feron *et al.* in preparaton

Guidelines and innovation

- If guidelines allow for a fully satisfactory treatment, we need no innovation…
- But what if innovation fulfills 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 others fail?
- Yes, if:
  - They are discovered and developed cheaply…
  - Their discovery/development uses 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** (see next slide)
- **1-year survival from cancer: € 2,000 to > € 70,000**

(based on my experience as a member of the Belgian Committee for Drug Reimbursement)

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]
1st 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
2nd 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)

Carbonnelle *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)
- **ATS**: American Thoracic Society (USA)
- **BAPCOC**: Belgian Antibiotic Policy Coordination Committee (Belgium)
- **BTS**: British Thoracic Society (United Kingdom)
- **CIO (SFN)**: Commissione Controllo Infezioni Ospedaliere (San Filippo Neri) (Italy)
- **DSMF/SLD/SYY**: Duodecim Societas Medicorum Fennica/Suomalaisen Lääkäriseuran Duodecimin/Suomen Lastenlääkäriyhdistyksen/Suomen Yleislääketieteen Yhdistys (Finland)
- **GOLD**: Global Initiative for Chronic Lung Obstructive Disease (International)
- **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 Portugesa 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