Prescribing guidelines in CAP: a global vision with a Russian perspective

Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology & Center for Clinical Pharmacy
Louvain Drug Research Institute,
Catholic University of Louvain
Brussels, Belgium

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

INSPIRATION: Global Perspectives and Local Insights in Infection Management
12th October 2013, Moscow, Russia

With thanks to Drs Sylviane Carbonelle, Ann Lismond, and Françoise Van Bambeke (co-authors) and to Prof. Roman Kozlov for introduction to the Russian guidelines

With approval of the Belgian Ethical Healthplatform – visa no. 13/V1/4123/054843

Disclosures

Financial support from

- the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
- *Université catholique de Louvain* for personal support
- Commercial Relationships:
  - 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

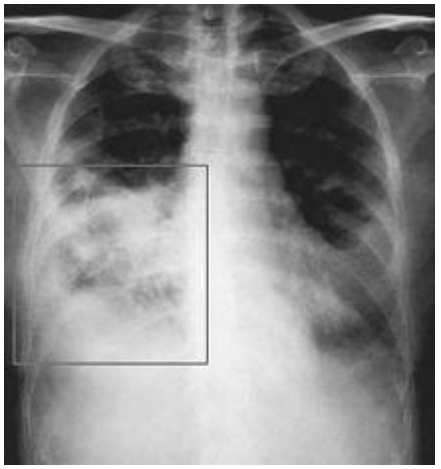
Service de Microbiologie, Faculté de Médecine, Institut de Botanique, Université de Liège, 4000 Sart Tilman, Liège, Belgium

and died from invasive pneumococcal infection …

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

Do we have a problem ?

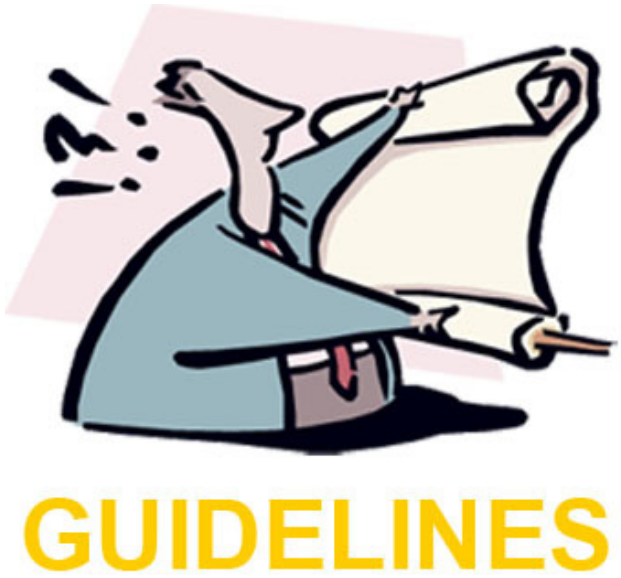
- CAP:
  - remains a major acute cause of death (3rd to 7th);
  - mortality varies from < 2% to 30% of more depending largely of co-morbidities, host defenses status, and age;
  - *Streptococcus pneumoniae* is the most commonly identified pathogen, but other bacteria may be critical in specific environments (the causative organisms remains, however, unidentified in 30% to 50% of cases).



CAP: community acquired pneumonia

What is my goal ?

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



CAP: community acquired pneumonia

Guidelines: origin, basis and use

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

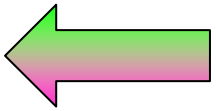
- Guidelines have been used since the beginning of medicine

- Modern medical guidelines are supposed to be based on **critical examination of current evidence**, with emphasis on **evidence-based** rather than eminence-based medicine

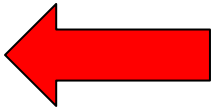
- More and more, healthcare professionals must not only know about, but **apply guidelines** or **justify why they do not follow them** for an individual patient or a group of patients

Guidelines: content and goals

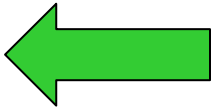
- Modern clinical guidelines should identify the **most valuable evidence** and integrate this knowledge to build **optimized decisions trees** that should be applicable to the **majority of patients**, while being sufficiently flexible to accommodate a sufficient level of **individual variation**



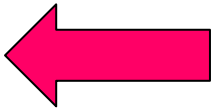
- But guidelines are also often seen as a mean to **standardize medical care** with 2 potential consequences/goals:



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

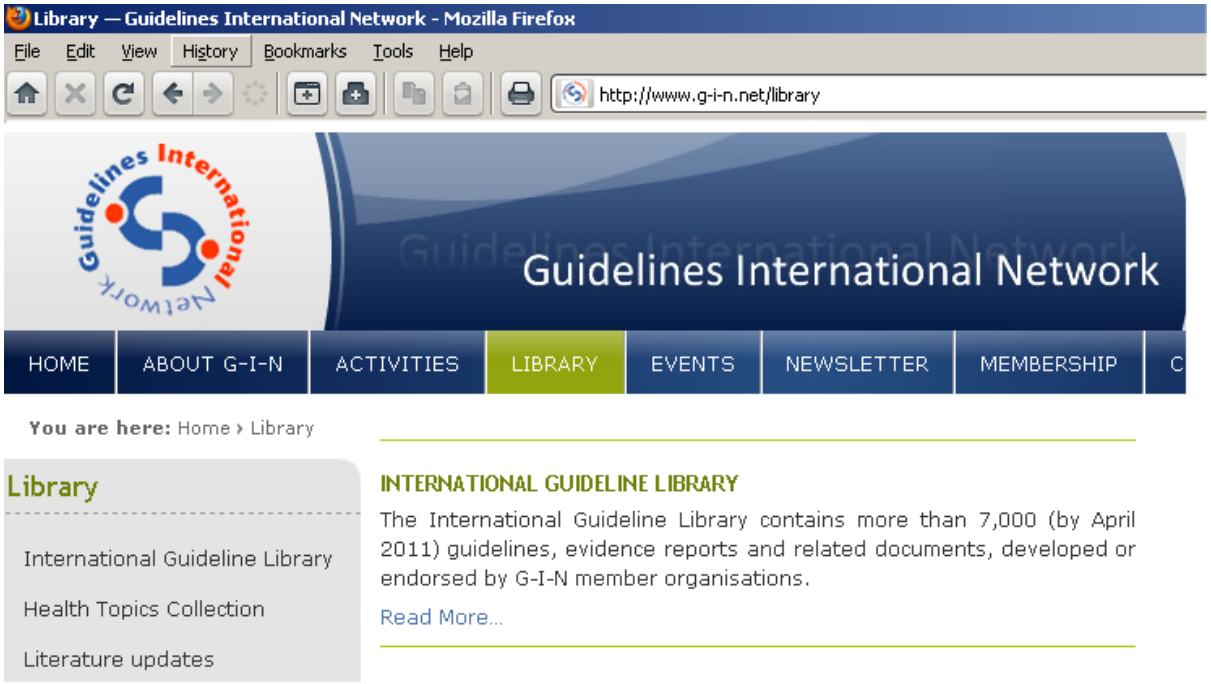


  - to achieve the **best balance between cost and medical efficacy** (broadly speaking)



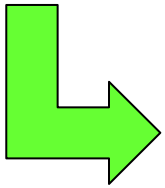
Guidelines: who and where?

- 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 be 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 (this version is available in Russian)
- Updated as version 2 in 2010 (Russian translation in progress)

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 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.

Did you really take the patient into consideration ?

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 development

1. Systematic methods w
2. The criteria for selectin
3. The strengths and limit
   describ
   ...s, sid
   ...ormulati
6. There is an explicit link
   supporting evidence.
7. The guideline has bee
   its publication.
8. **A procedure for updating the guideline is provided.**

using this map may not be the best way to find your way in Moscow !

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 (its application.**
2. The guideline p recommendatio
3. **The potential r recommendati**
4. **The guideline criteria.**

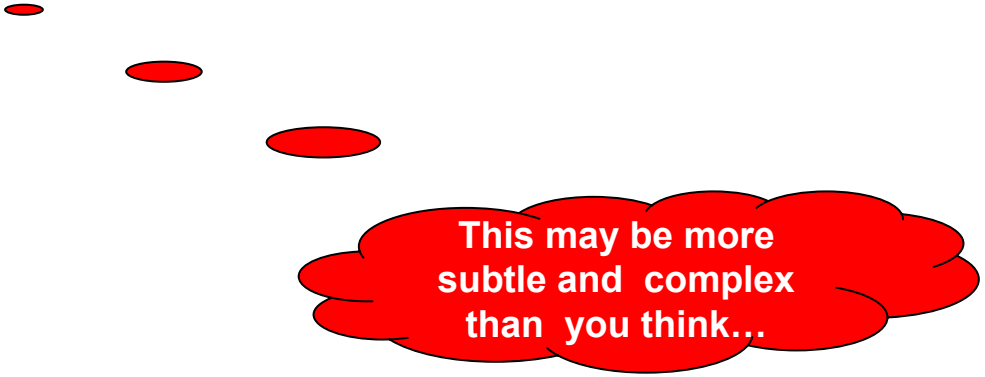
Can you find easily which connection is faulty ?

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.**

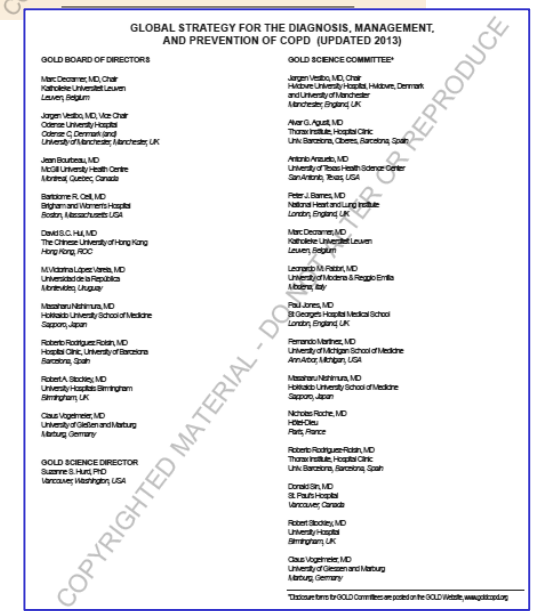


Editorial independence is more than declaring...

Global Initiative for Chronic Obstructive Lung Disease

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

UPDATED 2013


GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD (UPDATED 2013)

GOLD BOARD OF DIRECTORS

GOLD SCIENCE COMMITTEE*

GOLD SCIENCE DIRECTOR

Almirall
AstraZeneca
Boehringer Ingelheim
Chiesi
Forest Laboratories
GlaxoSmithKline
Grupo Ferrer
Merck Sharp and Dohme
Mylan
Nonin Medical
Novartis
Pearl Therapeutics
Pfizer
Quintiles
Takeda

INAMI .be

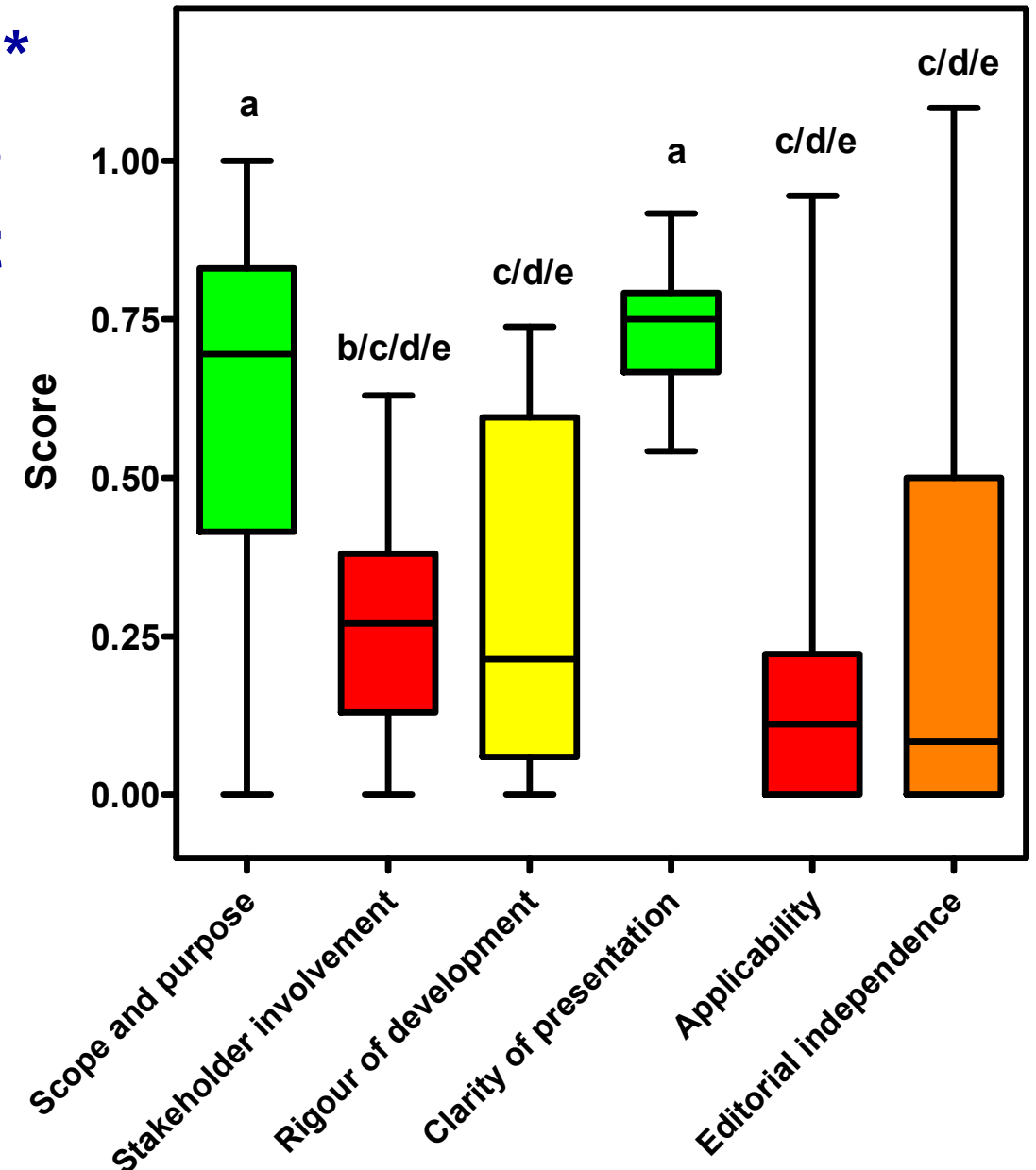
Belgian Social Security (payer)

Inhibiteurs de la pompe à protons et statines

Utilisation et prescription

Analysis of 30 CAP * guidelines with the AGREE Instrument

* CAP: community acquired pneumonia



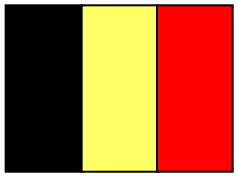
- Mean scores presented as 'boxes and whiskers' (lowest to highest with 25 -75% and median.
- Scores of domains with different letters are significantly different from each other (Kruskal-Wallis test with Dunn's Multiple Comparison Test)

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



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

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.

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

Guidelines: are they used?

Example 2: hospital practice

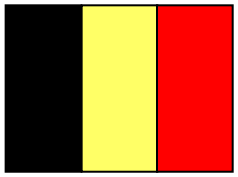
Journal of Antimicrobial Chemotherapy (2008) **62**, 189–195
doi:10.1093/jac/dkn143
Advance Access publication 8 April 2008

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

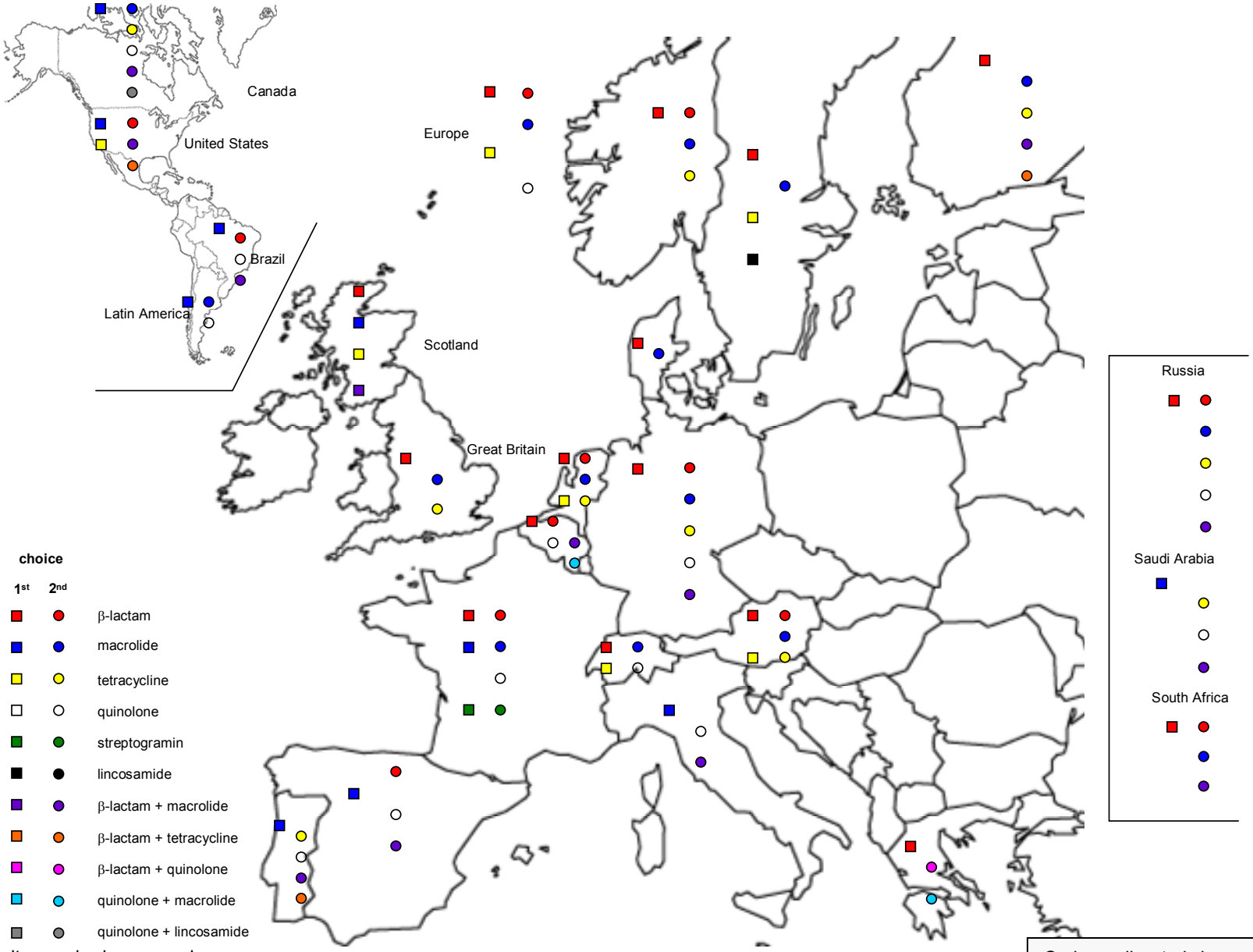
Conclusions: Locally developed hospital guidelines experience the same barriers as other guidelines. Within one hospital, prescribers have to be seen as a number of different target groups instead of a homogeneous population. For an optimal effect, interventions will have to consider these differences.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



CAP: community acquired pneumonia

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. Woodhead et al. Clin Microbiol Infect 2011; 17(Suppl. 6): E1–E59 – doi: 10.1111/j.1469-0691.2011.03672.x
2.Rev. Mal. Resp. 2003; 20:462-469 (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 Arch Bronconeumol. 2005;41(5):272-89 (http://www.archbronconeumol.org/en/pdf/13075322/S300/)
6. http://www.sppneumologia.pt/sites/sppneumologia.pt/files/pdfs/RPP_2005_3_243_Praticas.pdf

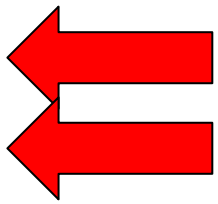
A comparison of two CAP guidelines separated by an ocean …

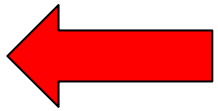
Clinical situation	North American guidelines	UK guidelines
Initial antibiotic choice for adults hospitalized with low-moderate severity CAP treated in the commu[nity]	• selected patients with no cardiopulmonary disease or modifying factors → **macrolide alone *** • outpatients with cardiopulmonary disease 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

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

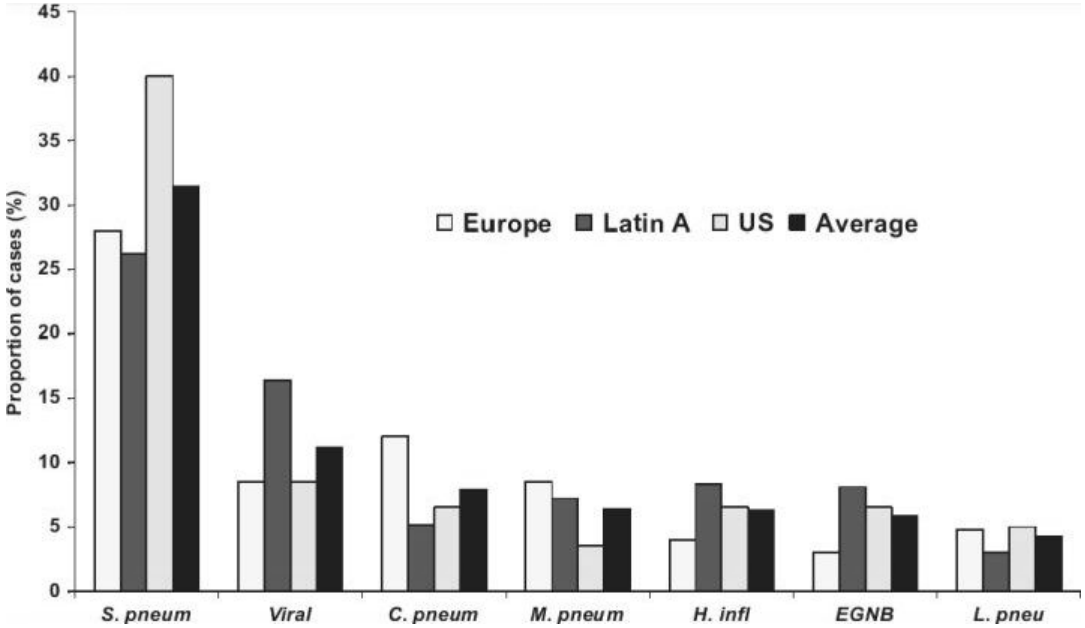
- How sure are you of the diagnosis ?
- **Which are the main pathogens ?**
- **What are their current resistance patterns ?**
- How should the therapy be initiated (empiric *vs.* directed) ?
- **Which level of adverse effects is acceptable ?**
- Which patients do you mainly treat?
- Does cost matter?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





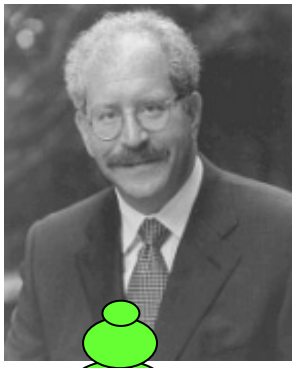
CAP: community acquired pneumonia
COPD: chronic obstructive pulmonary disease

Do CAP pathogens vary between countries/regions ?



Etiology of community-acquired pneumonia in Europe, Latin America, and the United States, and overall, according to published epidemiological studies aimed at reporting such etiology performed in more than 10,000 patients from Europe, Latin America, the United States, and on average in all those sites.

Niederman et al. Semin Respir Crit Care Med 2012; 33(03): 298-310



Prof. Niedeman says NO, but

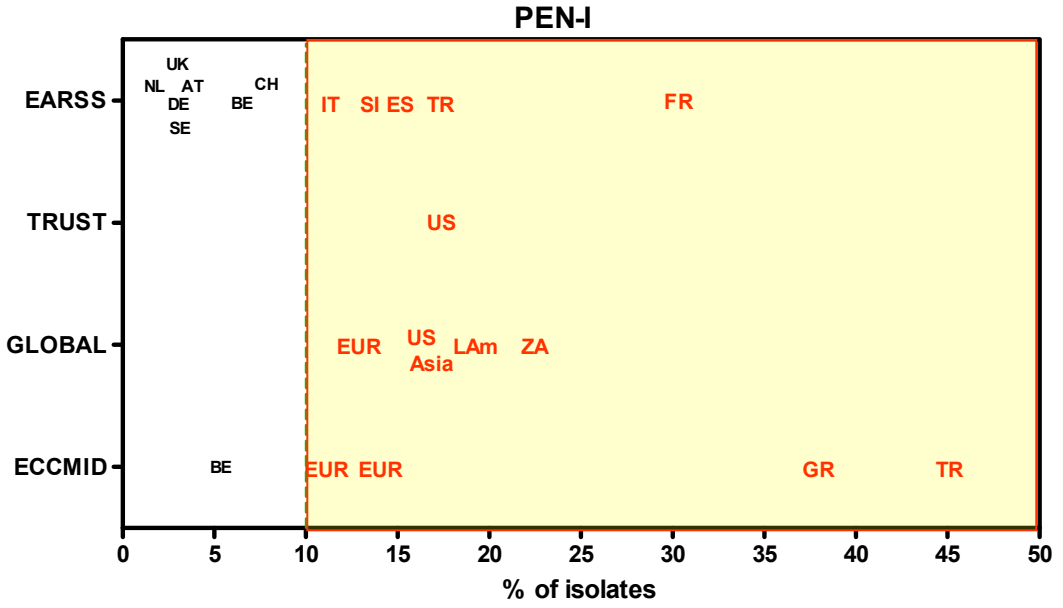
- **HIV/AIDS could impact...**
- **tuberculosis needs to be considered**
- **unusual pathogens (e.g. melioidosis in Southeast Asia)**

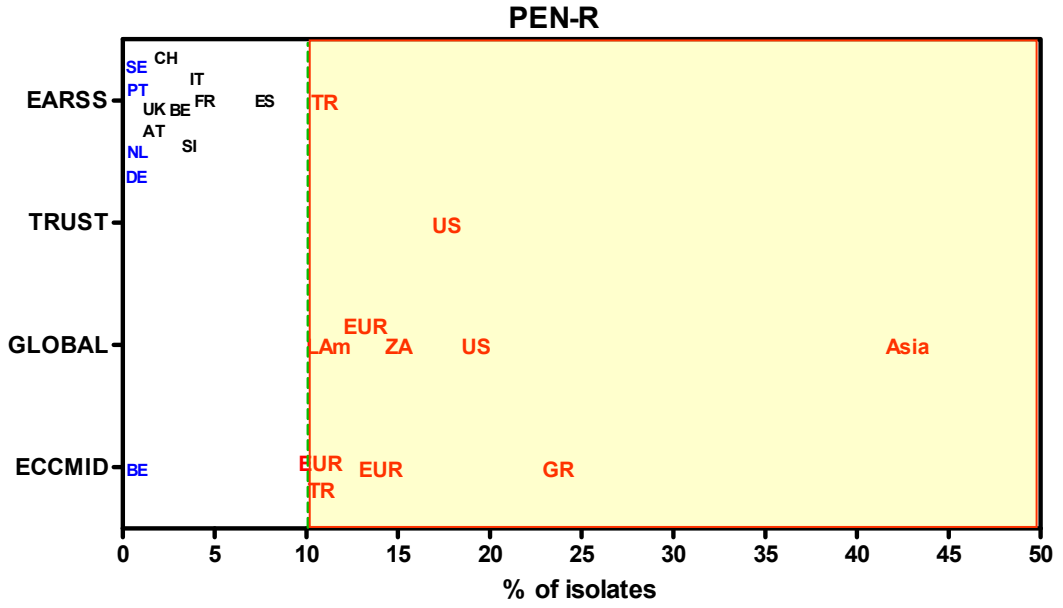
CAP: community acquired pneumonia

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





Lismond *et al.*, in preparation

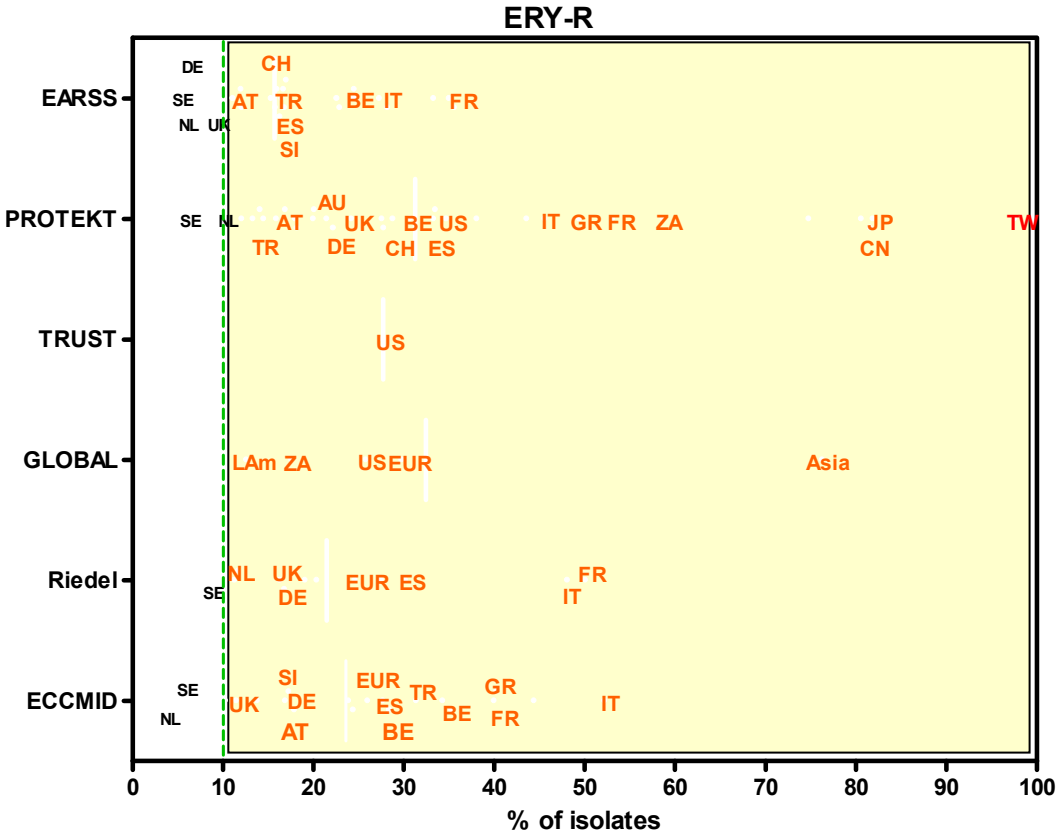
CAP: community acquired pneumonia

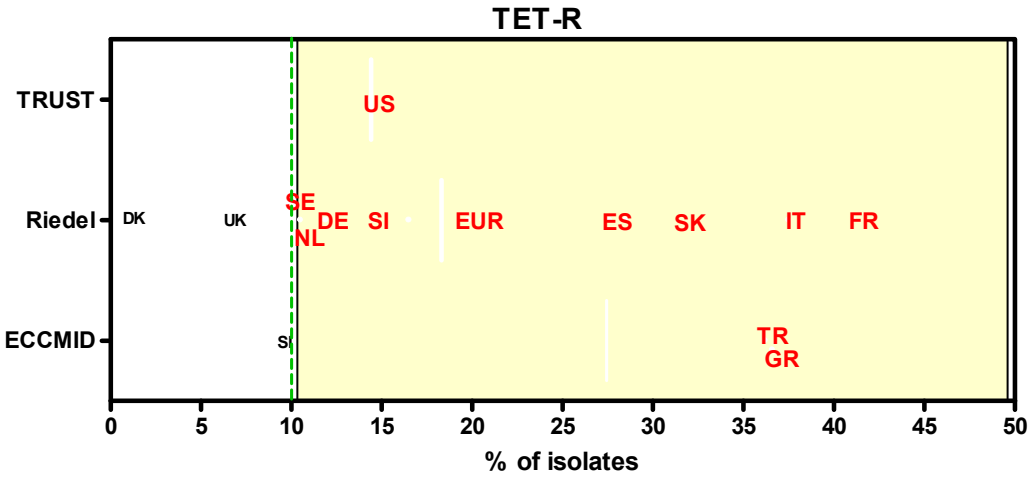
Resistance of *S. pneumoniae* *

*analysis of resistance of eryhromycin 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

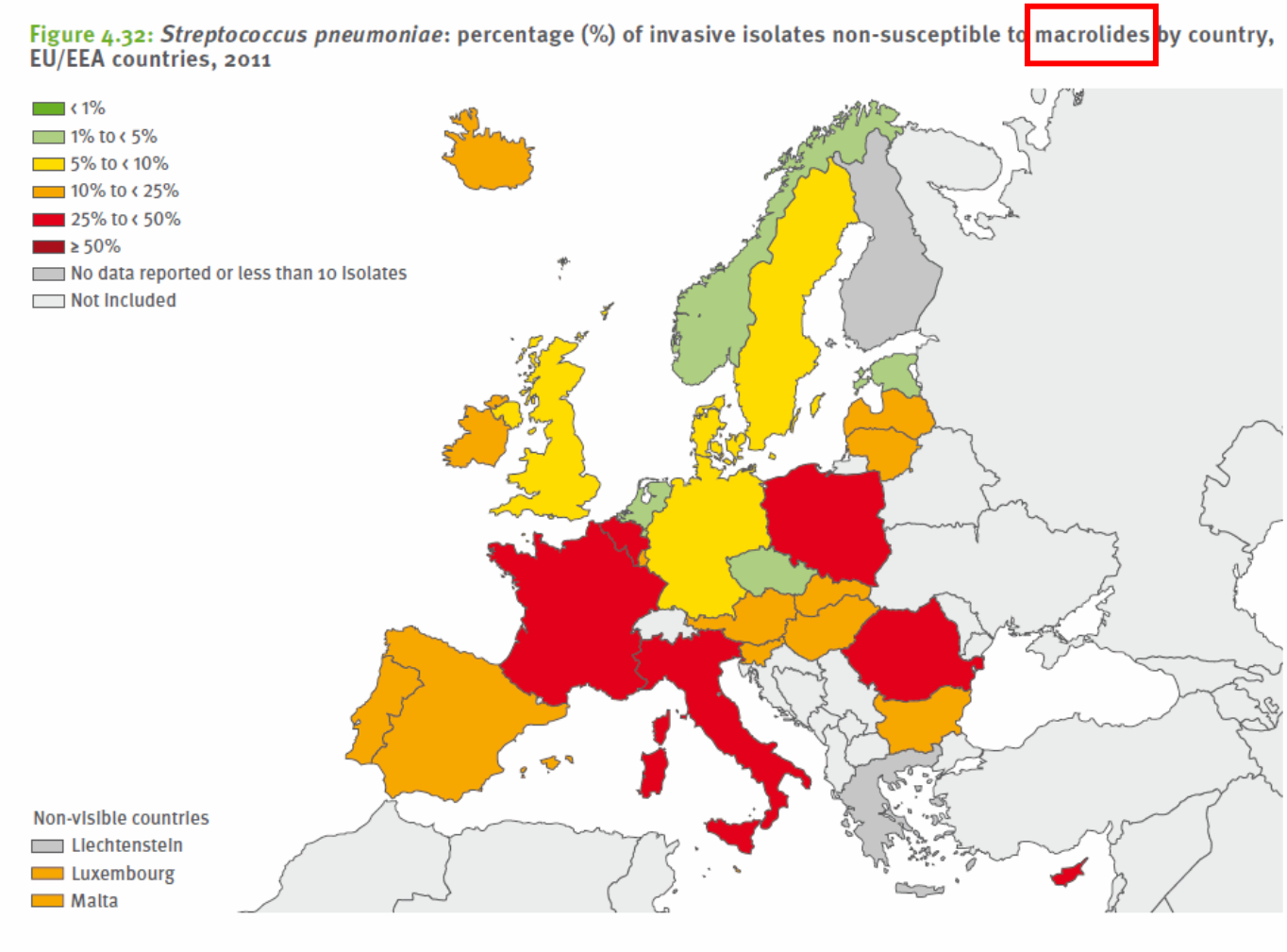
Lismond *et al.*, in preparation





The message: make and use surveillance studies

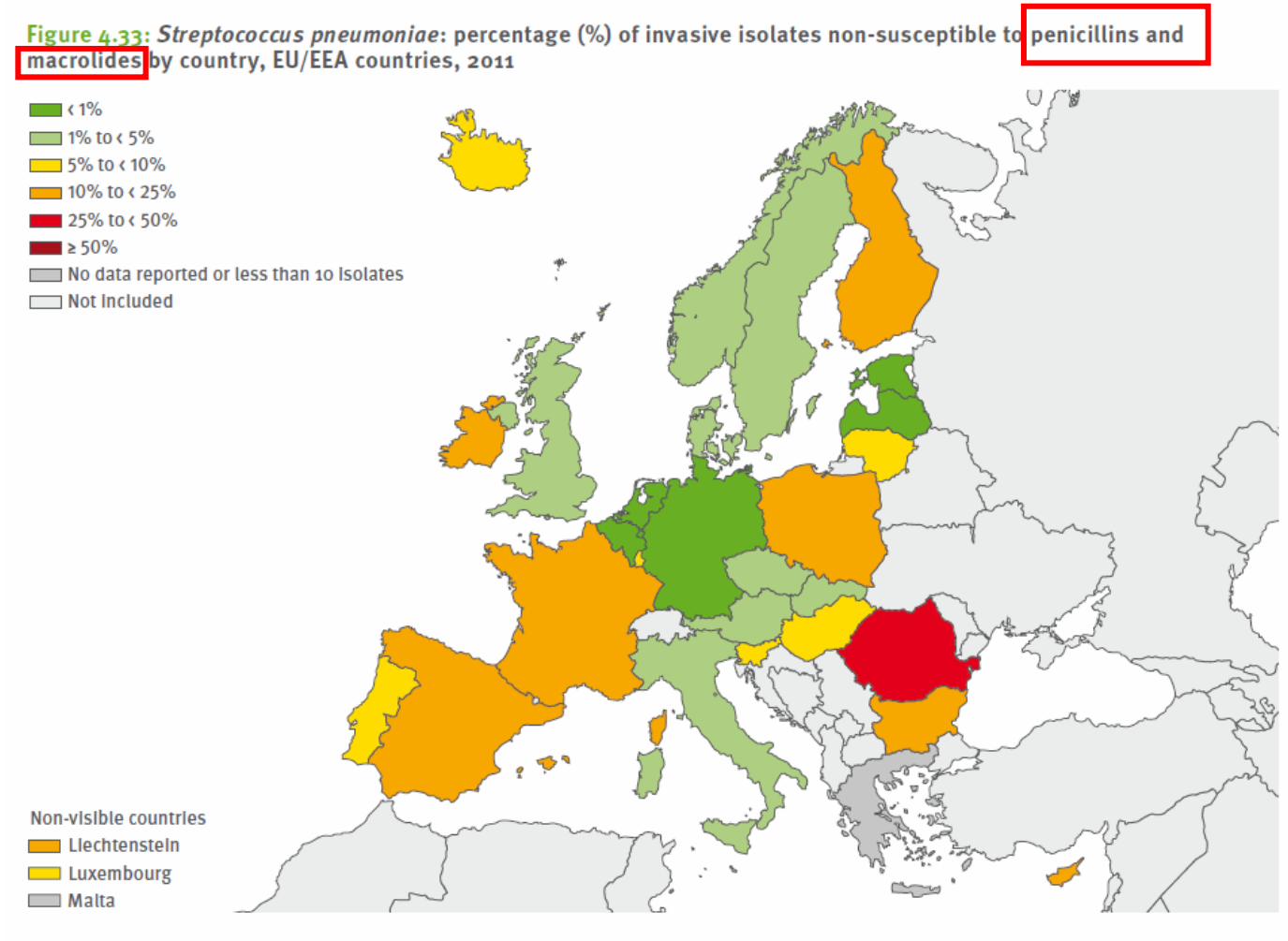
Countries / Regions should know THEIR resistance patterns !



European Antimicrobial Resistance Surveillance Network
http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx

The message: make and use surveillance studies

Countries / Regions should know THEIR resistance patterns !



European Antimicrobial Resistance Surveillance Network
http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx

Susceptibility of *S. pneumoniae*: Russian Data

УДК [579.862.04+616.98:579.862]-036.22

Динамика резистентности *Streptococcus pneumoniae* к антибиотикам в России за период 1999–2009 гг.

(*Результаты многоцентрового проспективного исследования ПеГАС*)

Р.С. Козлов, О.В. Сивая, О.И. Кречикова, Н.В. Иванчик
и Группа исследователей проекта «ПеГАС»
НИИ антимикробной химиотерапии, Смоленск, Россия

Рост резистентности *S. pneumoniae* к антибиотикам во многих странах определил необходимость проведения проспективного многоцентрового микробиологического исследования с централизованным определением чувствительности выделенных микроорганизмов в референтной лаборатории для получения достоверных и сопоставимых данных о резистентности *S. pneumoniae* в различных регионах России.

A central laboratory

Kozlov PC, et al. Clin Antimicrob Chemother 2010;12:329-41

Susceptibility of *S. pneumoniae*: Russian Data

УДК [579.862.04+616.98:579.862]-036.22

Динамика резистентности *Streptococcus pneumoniae* к антибиотикам в России за период 1999–2009 гг.

(*Результаты многоцентрового проспективного исследования ПеГАС*)

Р.С. Козлов, О.В. Сивая, О.И. Кречикова, Н.В. Иванчик
и Группа исследователей проекта «ПеГАС»
НИИ антимикробной химиотерапии, Смоленск, Россия

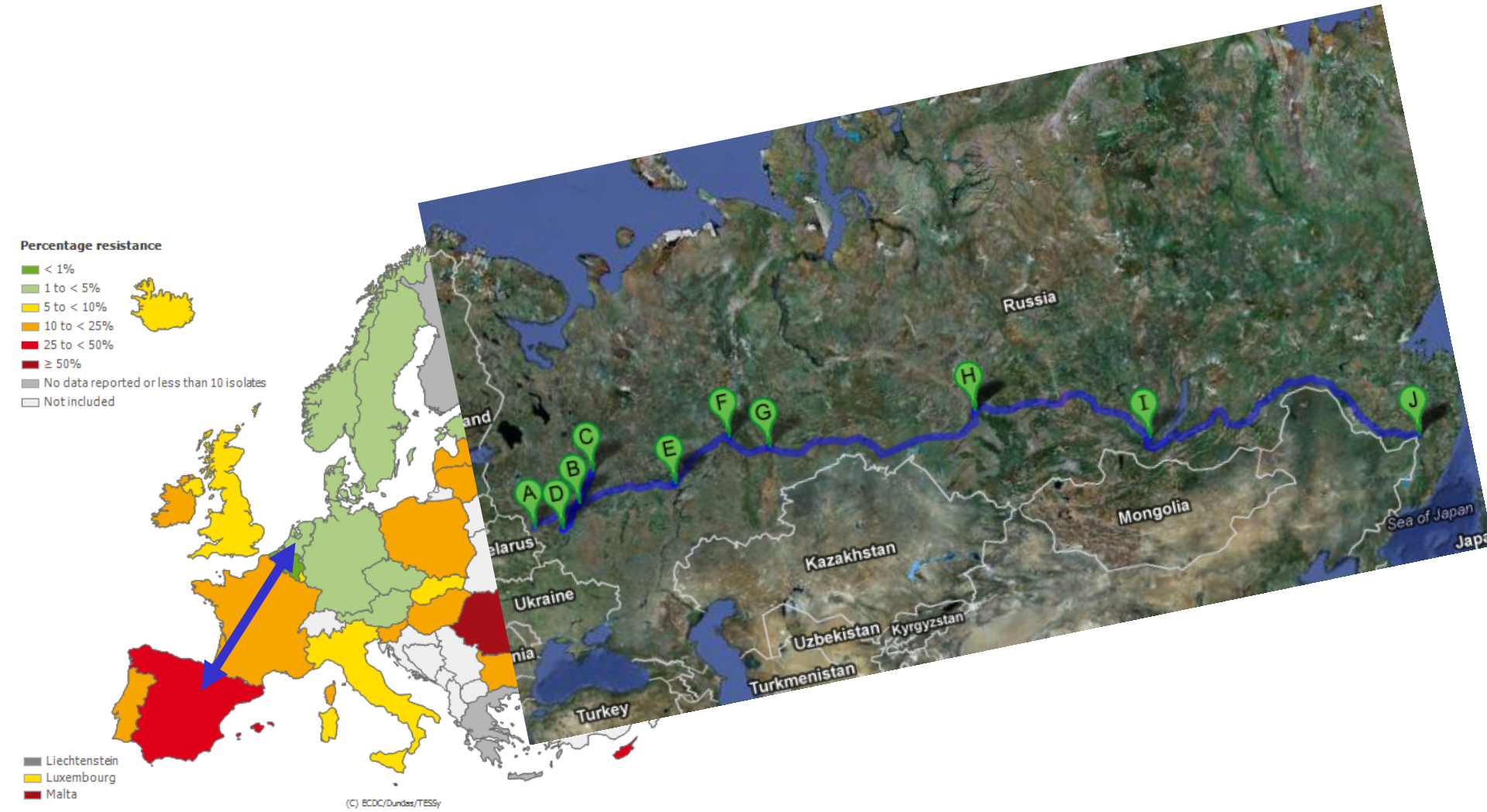
Geographical diversity

Рост резистентности *S. pneumoniae* к антибиотикам во многих странах определил необходимость провед… робиол… ным о… микро… получе… резист… Росси…

В 2006–2009 гг. в исследовании участвовали 14 центров Центрального (Москва – 2 центра, Смоленск, Ярославль, Калуга), Южного (Краснодар), Приволжского (Казань, Пермь), Уральского (Екатеринбург – 3 центра), Сибирского (Иркутск, Томск) и Дальневосточного (Хабаровск) федеральных округов России.

Kozlov PC, et al. Clin Antimicrob Chemother 2010;12:329-41

A long but very useful trip



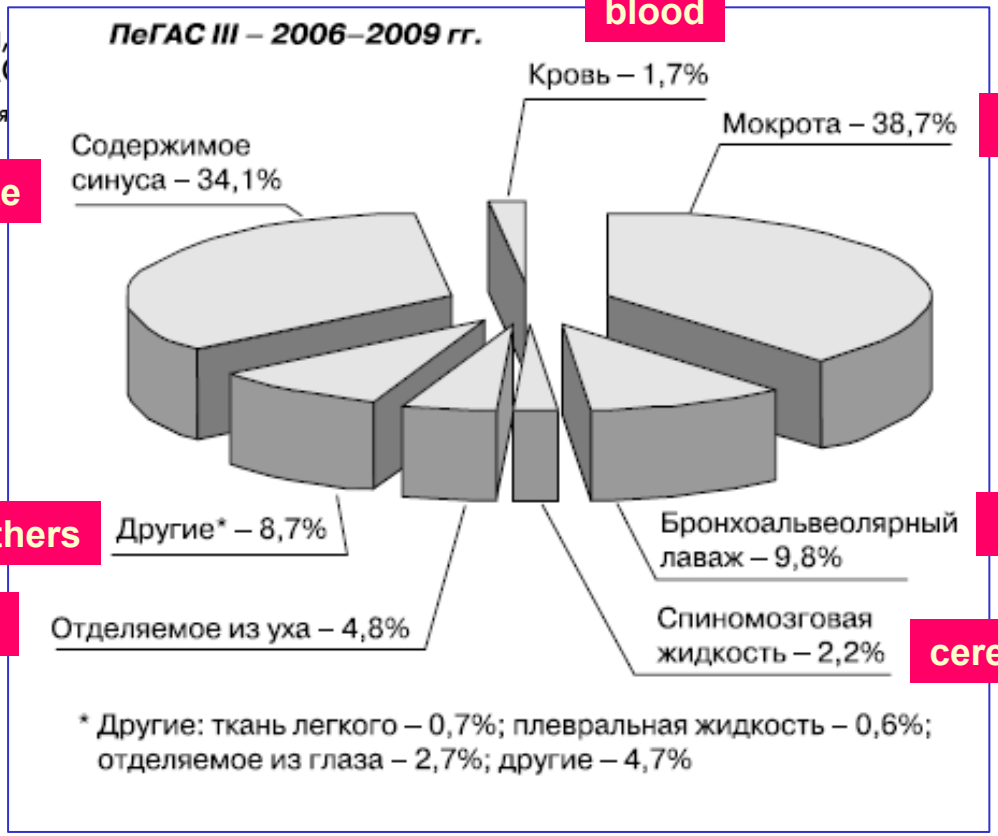
Susceptibility of *S. pneumoniae*: Russian Data

УДК [579.862.04+616.98:579.862]-036.22

Динамика резистентности *Streptococcus pneumoniae* к антибиотикам в России за период 1999–2009 гг.

(*Результаты многоцентрового проспективного исследования ПеГАС*)

Р.С. Козлов, О.В. Сивая, О.И. Кречикова,
и Группа исследователей проекта «ПеГА
НИИ антимикробной химиотерапии, Смоленск, Россия



blood

sputum

sinus aspirate

others

BAL

middle ear fluid

cerebrosp. fluid

Kozlov PC, et al. Clin Antimicrob Chemother 2010;12:329-41

A mots useful presentation: Russian Data

УДК [579.862.04+616.98:579.862]-036.22

Динам
pneum
за пер
(*Результа*

Р.С. Козлов
и Группа ис
НИИ антимикр

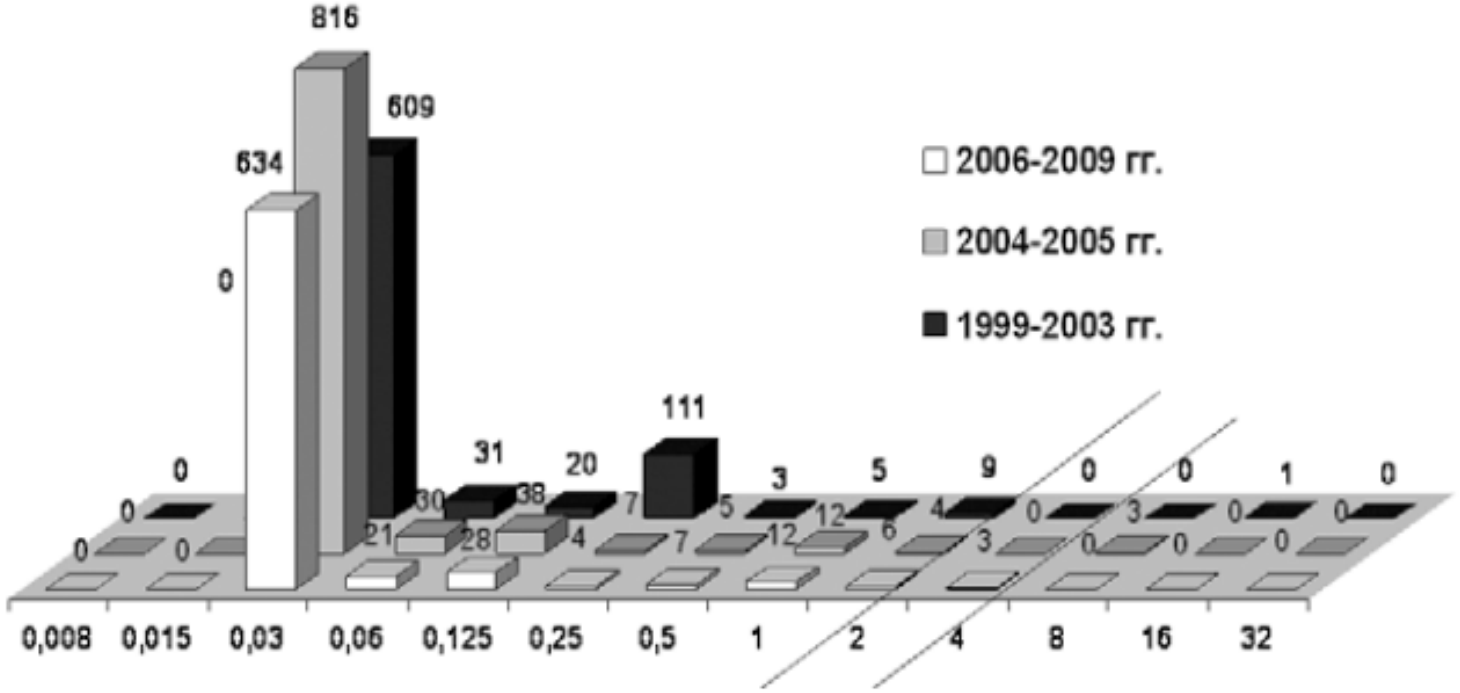


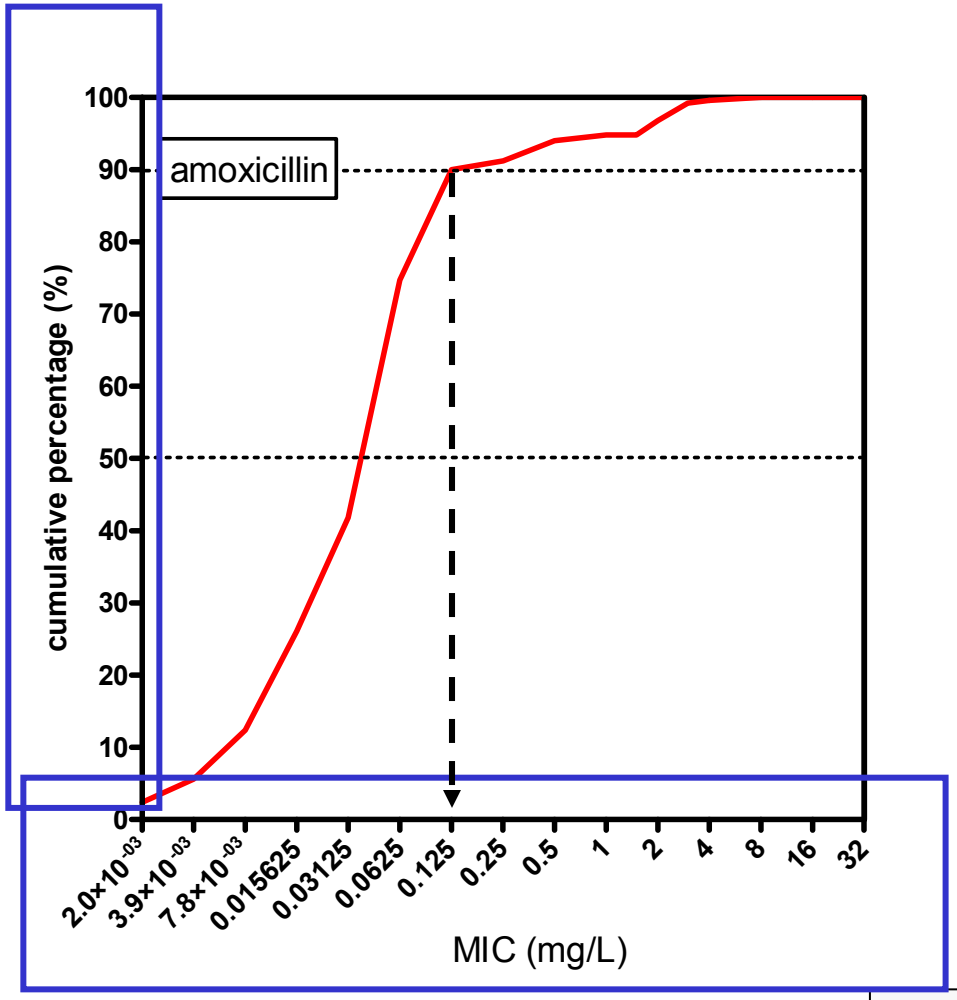
Рис. 3. Динамика распределения МПК амоксициллина, амоксициллина/клавуланата, амоксициллина/сульбактама для штаммов *S. pneumoniae* в исследуемые периоды.

Kozlov PC, et al. Clin Antimicrob Chemother 2010;12:329-41

But which breakpoints to use ?

To be honest, I always wondered ...

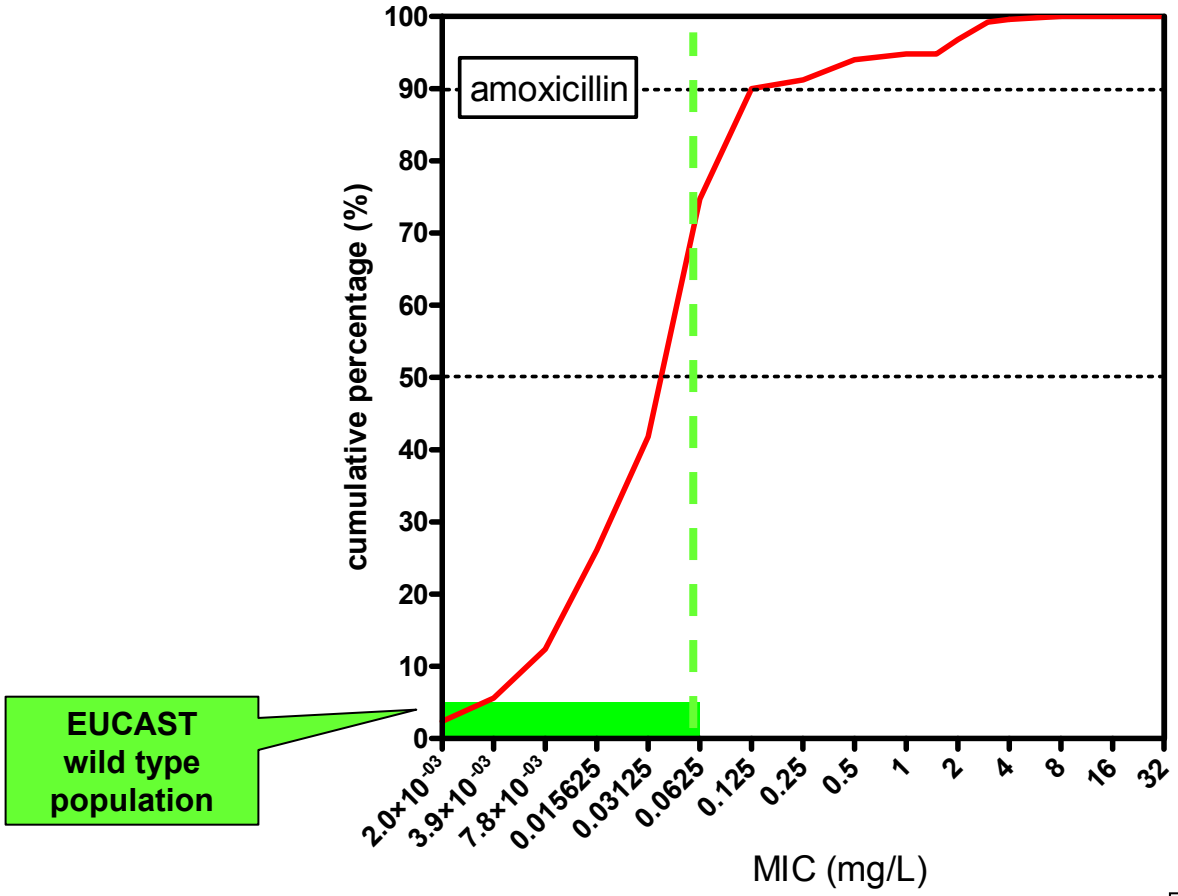
MICs are a continuous variable…



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

MIC: minimum inhibitory concentration

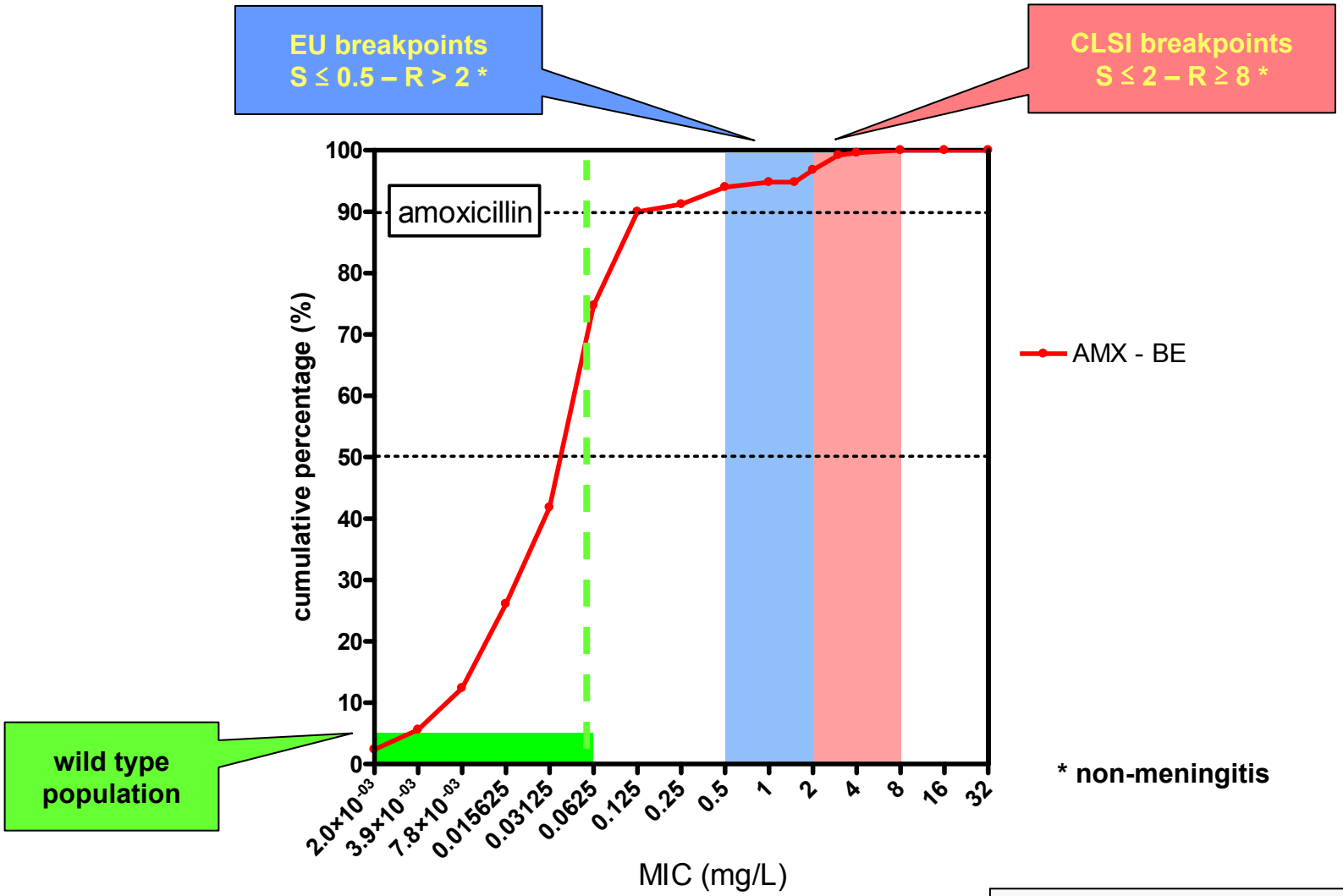
MICs are a continuous variable…
on which you can add information…



Belgian data (2007-2010):
Lismond et al. Int. J. Antimicrob Agents. 2012 Mar;39(3):208-16.

MIC: minimum inhibitory concentration

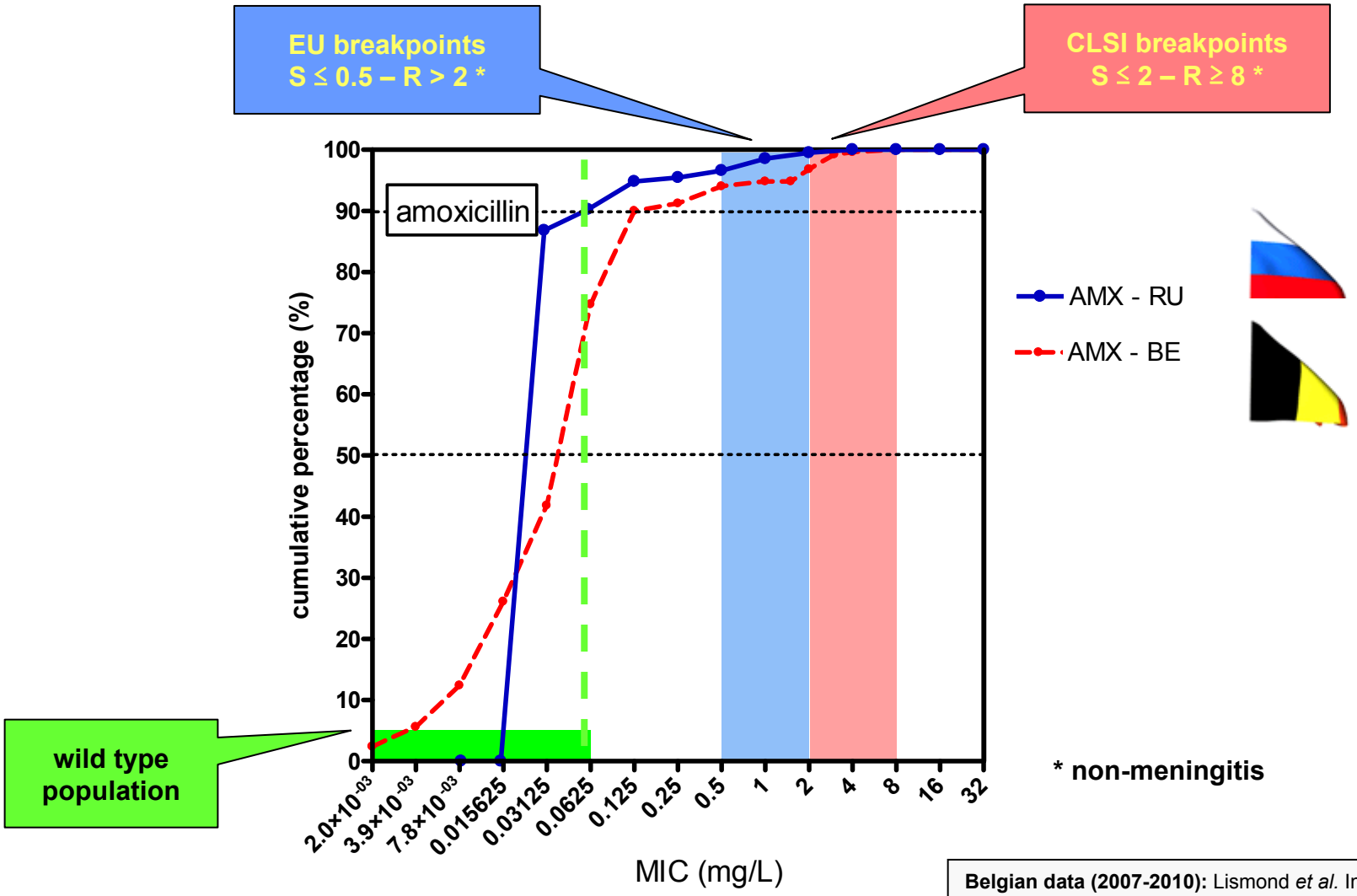
MICs are a continuous variable…
on which you can add information…



MIC: minimum inhibitory concentration
S: susceptible
R: resistant
AMX: amoxicillin

Belgian data (2007-2010):
Lismond et al. Int. J. Antimicrob Agents. 2012 Mar;39(3):208-16.

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

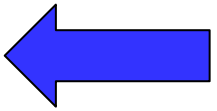


MIC: minimum inhibitory concentration
S: susceptible
R: resistant

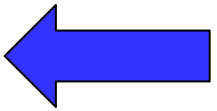
Belgian data (2007-2010): Lismond *et al.* Int. J. Antimicrob Agents. 2012 Mar;39(3):208-16.
Russian data (2006-2009): redrawn from Koslov *et al.* Clin Antmicrob Chemohher. 2010; 12:329–341.

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

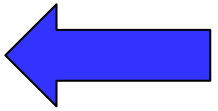
- With the new CLSI breakpoint (MIC ≥ 8 mg/L), very few isolates will be defined as resistant….



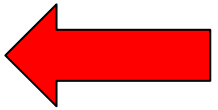
- In fact, most experts believe that CAP caused by organisms with a penicillin MIC of 4 mg/L or higher (still an uncommon finding), can lead to an increased risk of death.[1]



- 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 mg/L (➔ 0.5 g TID, 1 g TID, …)**
  ... but this may be necessary in Russia…

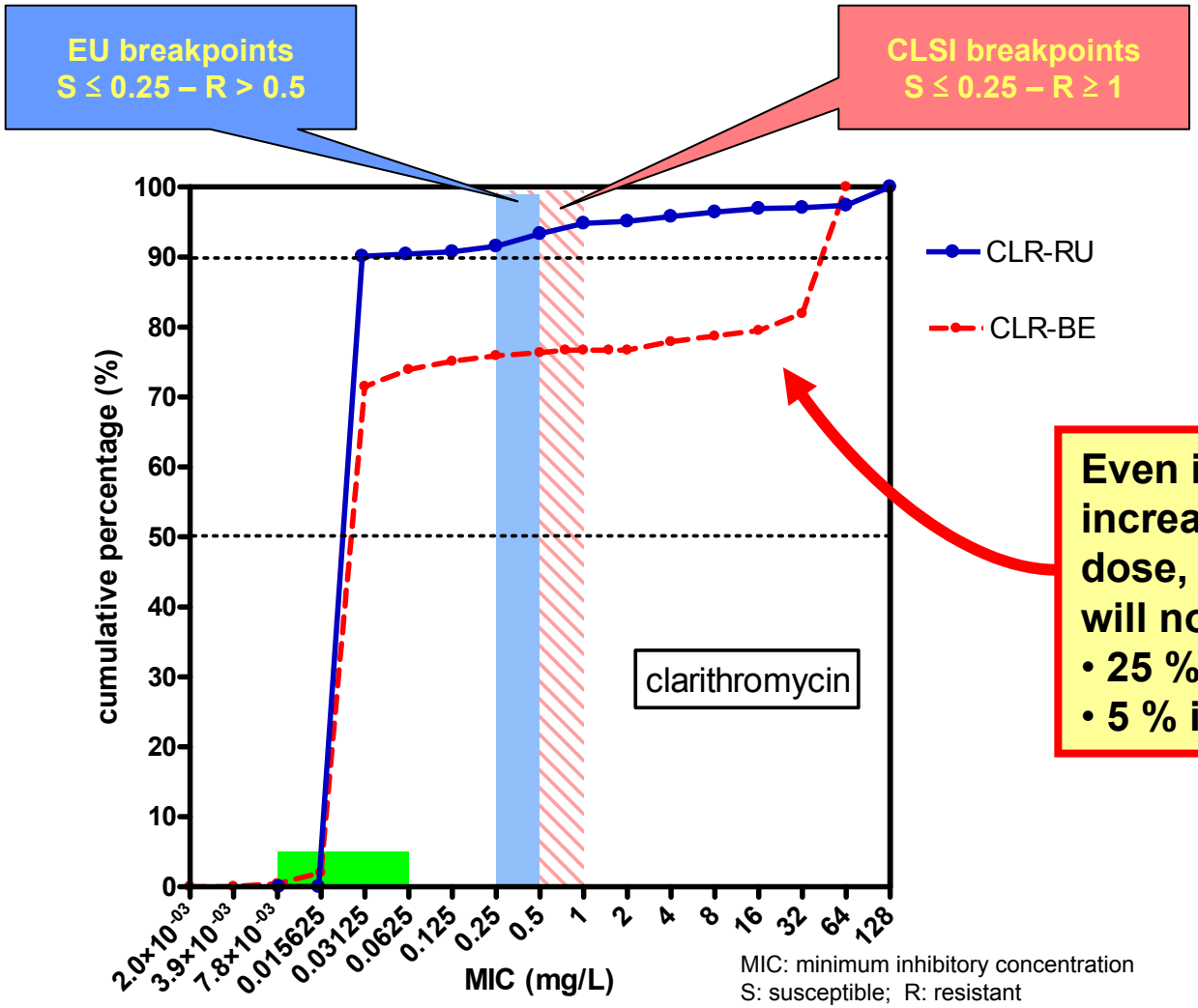


MIC: minimum inhibitory concentration
CAP: community acquired pneumonia
R: resistance
BID: twice daily; TID: 3 times daily

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 and in Russia



Even if you try increasing the dose, these isolates will not be covered
- **25 %in Belgium**
- **5 % in Russia**

MIC: minimum inhibitory concentration
S: susceptible; R: resistant
CLR: clarithromycin

Belgian data (2007-2010): Lismond *et al.* Int. J. Antimicrob Agents. 2012 Mar;39(3):208-16.
Russian data (2006-2009): redrawn from Koslov *et al.* Clin Antmicrob Chemother. 2010; 12:329–341.

But a divergent view... (ancient ?)

JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 2003, p. 4906 Vol. 41, No. 10
0095-1137/03/$08.00+0 DOI: 10.1128/JCM.41.10.4906.2003

Macrolide Resistance in *Streptococcus pneumoniae* Strains Collected in the Far East of Russia from 2000 to 2002

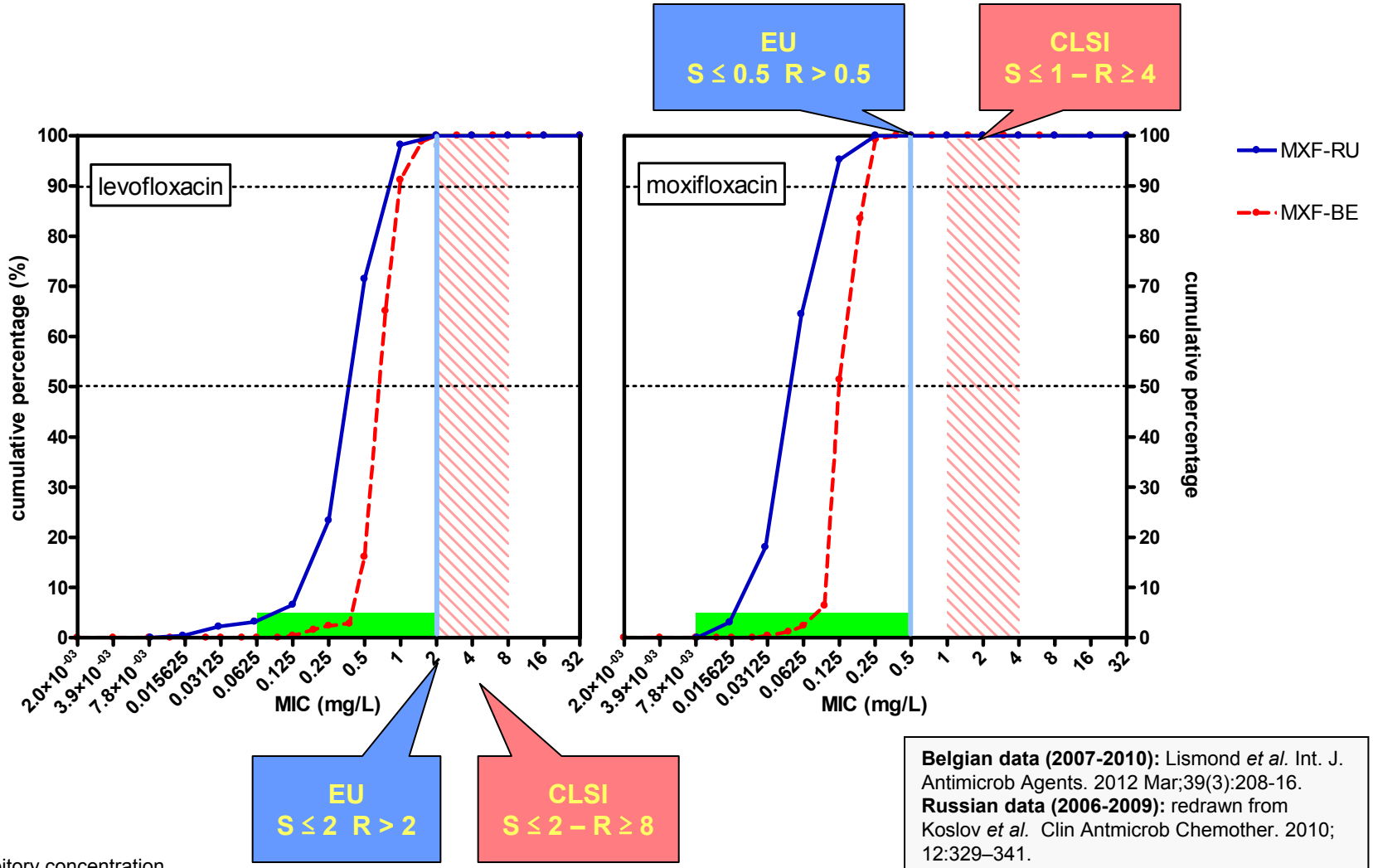
Alina V. Martynova, Vyacheslav B. Turcutyuicov

A total of 35.82% (48 of 134 strains) of the *S. pneumoniae* strains were resistant to erythromycin with a MIC of ≥1.0μg/ml. Of these, 31.25% (15of 48) showed an MLS_B phenotype with erythromycin and clindamycin 50% MICs (MIC_{50}s) and MIC_{90}s of >64 μg/ml; 66.6% (32 of 48) showed resistance to erythromycin alone (M phenotype), with a MIC_{50} and MIC_{90} of 8.0 μg/ml. One isolate was postive with both *ermB* and *mefE* primers.

this is more akin to Belgium ...

And for respiratory fluoroquinolones ?

Susceptibility profile of *S. pneumoniae* to levofloxacin and moxifloxacin in Belgium and in Russia



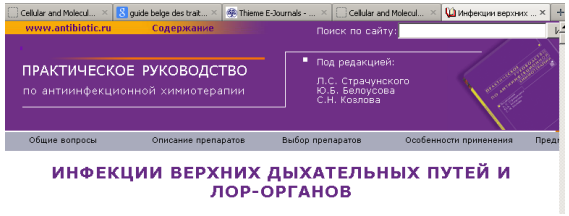
S: susceptible
R: resistant
MXF: moxifloxacin
MIC: minimum inhibitory concentration

Belgian data (2007-2010): Lismond *et al.* Int. J. Antimicrob Agents. 2012 Mar;39(3):208-16.
Russian data (2006-2009): redrawn from Koslov *et al.* Clin Antmicrob Chemother. 2010; 12:329–341.

Comparing guidelines

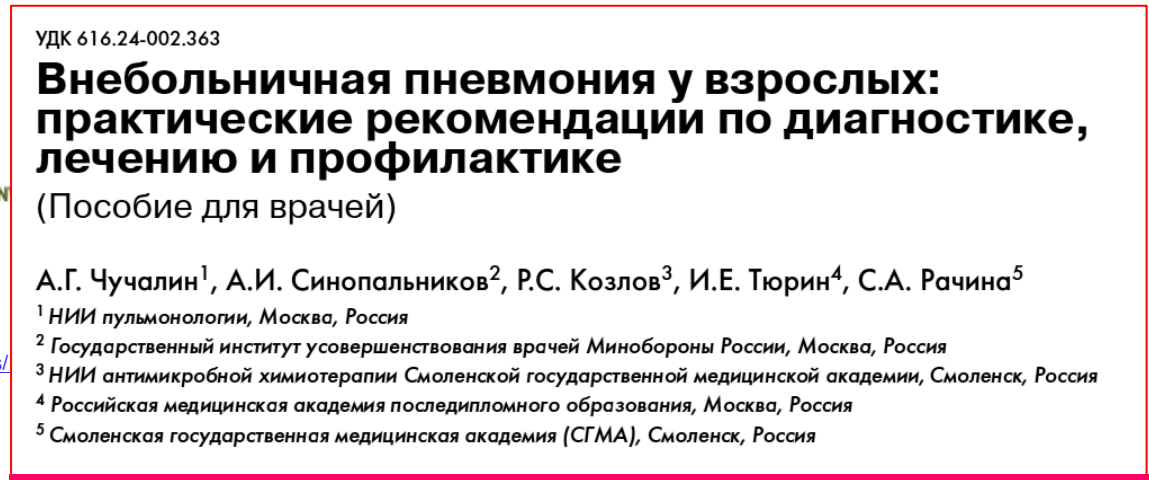
http://www.health.belgium.be/eportal/Myhealth/Care/Properuse/Antibiotics/15616531_FR?ie2Term=Guide%20belge%20des%20traitements%20anti-infectieux%20en%20pratique%20ambulatoire&ie2section=83

http://www.antibiotic.ru/ab/085-89.shtml



Comparing guidelines

http://www.health.belgium.be/eportal/Myhealth/Care/Properuse/Antibiotics/6531_FR?ie2Term=Guide%20belge%20des%20traitements%20anti-infectieux%20en%20pratique%20ambulatoire&ie2section=83



УДК 616.24-002.363

Внебольничная пневмония у взрослых: практические рекомендации по диагностике, лечению и профилактике

(Пособие для врачей)

А.Г. Чучалин[1], А.И. Синопальников[2], Р.С. Козлов[3], И.Е. Тюрин[4], С.А. Рачина[5]

[1] *НИИ пульмонологии, Москва, Россия*

[2] *Государственный институт усовершенствования врачей Минобороны России, Москва, Россия*

[3] *НИИ антимикробной химиотерапии Смоленской государственной медицинской академии, Смоленск, Россия*

[4] *Российская медицинская академия последипломного образования, Москва, Россия*

[5] *Смоленская государственная медицинская академия (СГМА), Смоленск, Россия*

Community-acquired pneumonia in adults: practical guidance on the diagnosis, treatment and prevention (Manual for Physicians)
AG Chuchalin, AI Sinopalnikov, RS Kozlov, IE Tyurin, SA Rachina
***Clin Microbiol Antimicrob Chemother*. 2010;12(3):186–225**

Comparing guidelines (CAP / oral) : 1. Categories

Belgium

- **no comorbidity*, low lethal risk* and no pejorative condition *****
  - ***S. pneumoniae***
- **if comorbidities**
  - ***S. pneumoniae***
  - ***H. influenzae***

* COPD; diabetes; renal, hepatic or neurological disease; cardiac insufficiency; cancer

** lethal risk: resp. freq. 30/min ; art. press. < 90/60 mmHg; température > 40C o' < 35C; confusion; cyanosis; heart rate > 125/min

*** pejorative conditions: age >65 years, previous hospitalization for pneumonia, recent antibiotic treatment, unfavouravle socioeconomic status, poor compliance; severe emesis

Russia

- **no concomitant disease and no antimicrobials since 3 months**
  - ***S. pneumoniae***
  - ***M. pneumoniae***
  - ***Clamidophila pneumoniae***
  - ***H. influenzae***
- **concomitant disease or with antimicrobials since 3 months**
  - ***S. pneumoniae***
  - ***H. influenzae***
  - ***S. aureus***
  - ***Enterobacteriaceae***

CAP: community acquired pneumonia

Guide Belge des traitements anti-infectieux en pratique ambulatoire (http://www.health.belgium.be)
Chuchalin AG *et al*. *Clin Microbiol Antimicrob Chemother*. 2010;12(3):186–225.

Comparing guidelines (CAP / oral): 2. Antibiotics

Belgium

- no comorbidity, low lethal risk and no pejorative condition
  - amoxicilline 1 g q8h
- if comorbidity:
  - amoxicillin-clavulanic acid
- if non-IgE-mediated allergy to penicillin:
  - cefuroxime axetil
- if IgE-mediated allergy to penicillin
  - moxifloxacin 400 mg/day
- if no improvement within 48 h
  - add a macrolide (clarithromycin, azithromycin)

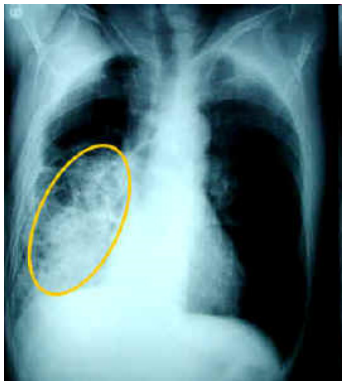
Russia

- no concomitant disease and no antimicrobial since 3 months
  1. amoxicilline or macrolide
  2. respiratory fluroquinolone (LVX / MXF)
- concomitant disease or with antimicrobial since 3 months
  1. amoxicilline-clavulanate
  2. respiratory fluoroquinolone (LVX / MXF)

CAP: community acquired pneumonia
LVX: levofloxacin
MXF: moxifloxacin

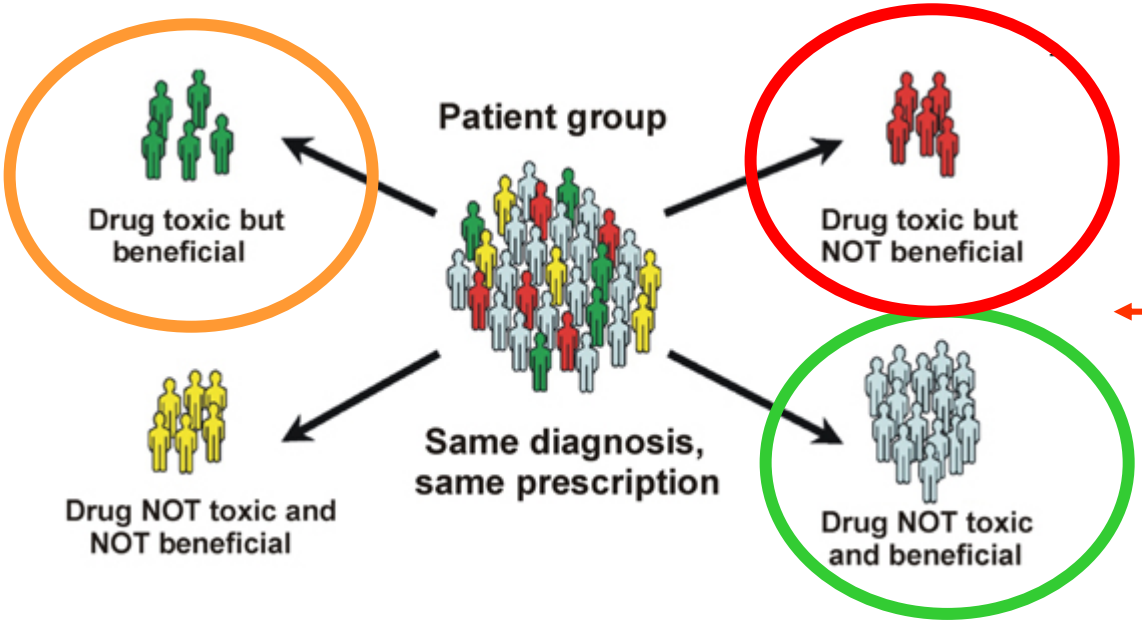
Guide Belge des traitements anti-infectieux en pratique ambulatoire (http://www.health.belgium.be)
Chuchalin AG *et al*. *Clin Microbiol Antimicrob Chemother*. 2010;12(3):186–225.

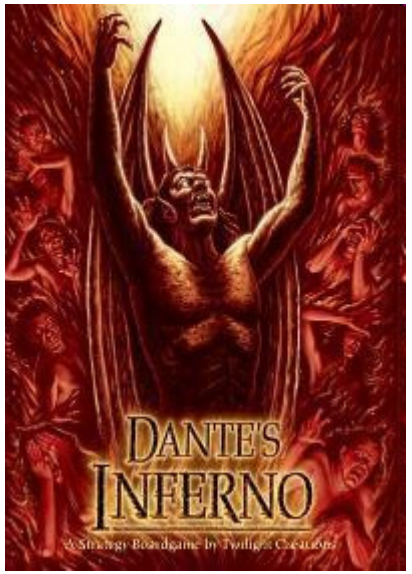
But what about side effects…



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 (European SmPC or equivalent)

Carbonelle et al. , 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 (European SmPC or equivalent)

Carbonelle et al. , 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 (ALT-AST elevation [common])** • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Musculoskeletal: tendinopathies** • Peripheral neuropathy • Prolongation of the QTc interval (cardiac disorders [rare]) • **Hypoglycaemia (rare)** • **Digestive tract: nausea, diarrhoea**
	moxifloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • **Hepatotoxicity (ALT-AST elevation [common])** • **Musculoskeletal: Tendinopathies** • Peripheral neuropathy • Prolongation of the QT interval (cardiac disorders [rare]) • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Digestive tract: nausea, diarrhoea**

* based on an analysis of the current respective labelling (European SmPC)
- common: 1/10 to 1/100
- rare: 1/1000-1/10000

Note: the current EU SmPCs of levofloxacin (TAVANIC®) and of moxifloxacin state:

- *For [community-acquired pneumonia], TAVANICc should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.*
- *Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.*

Carbonelle *et al.* , in preparation

All antimicrobials have associated risks

Conclusions so far:

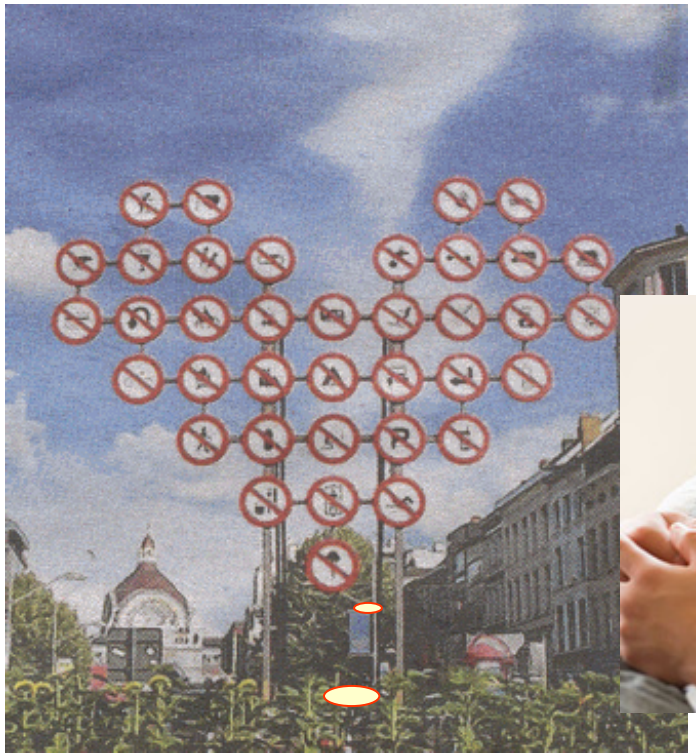
- All antimicrobials used in RTI are associated with known toxicities
- The main point will be the recognition of patients at risk (exclusions)
- The next point will be a correct evaluation of the benefit / risk ratio in the **specific environment** and for the **specific patient**

Never say that …

and check for specific risks

RTI: respiratory tract infection

The 3 major "points for attention" in guidelines



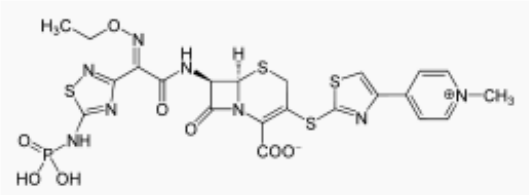
Are they not too dogmatic ?

Are they geared to the REAL patient ?

Are they regularly updated and modernized ?

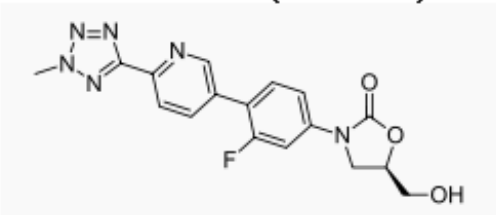
Modernization: do you know those (and what will you do with them) ?

Ceftaroline fosamil



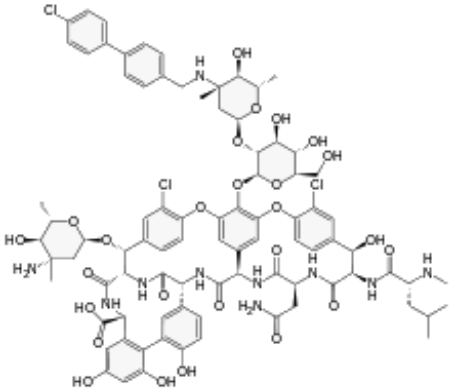
already available in Russia …

Tedizolid (torezolid)



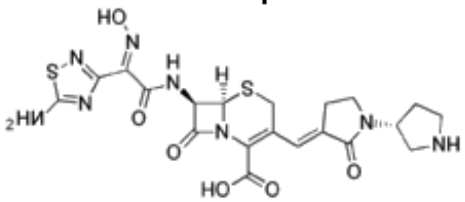
A "next generation" oxazolidinone

Oritavancin



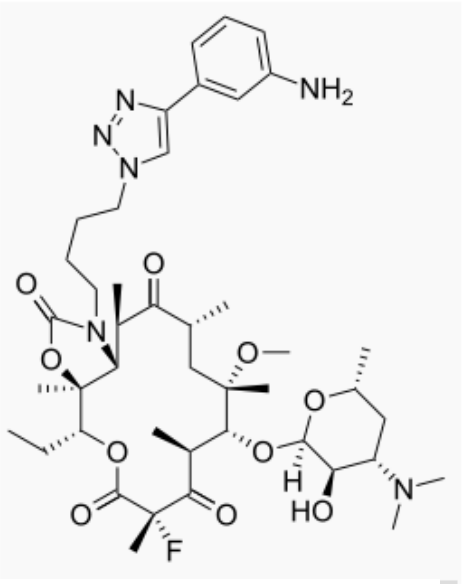
A "one injection" bactericidal lipoglycopeptide

Ceftobiprole



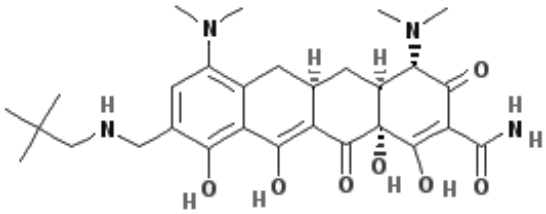
The 1st anti-MRSA cephalosporin…

Solithromycin



A "next generation" ketolide

omadacycline



A "tigecycline-like" drug for community infections

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)… that **never ends** (no suprize either) …
- They MUST remain open to accommodate for local and special situations, with the primary emphasis on **epidemiology** and the second on **real patients**…
- 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…**