What makes an antibiotic the right antibiotic ?

A story around respiratory tract infections

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10th Asia-Pacific Respiratory Tract Infections Forum, Taipei, Taiwan

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- Speaker's honoraria
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  - Flemish Education Program on Antibiotics *(Opleidingsprogramma Antibioticabeleid Vlaanderen)*

- Advisory Committees and Decision-making Bodies
  - US National Institutes of Health (*grant reviewing*)
  - General Assembly and former member of the Steering committee of EUCAST
  - External expert for the European Medicines Agency (EMA)
  - Former member Belgian Drug Reimbursement Committee (*CRM* / *CTG*)
  - Member of the Belgian Antibiotic Policy Coordination Committee (BAPCOC)
  - Governance of the EU program "DRIVE AB" (new economical framework for antibiotics)

Slides: http://www.facm.ucl.ac.be → Lectures

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

We do have guidelines but…

- we see **contradictions**
  - between countries
  - between experts
- they may **lack of update** for
  - shifts in resistance patterns
  - approval of new antibiotics
- they are often **out of "real practice"**
- they assume a **definite diagnostic**

- **I presented in 2013 at the 7th RTI forum a detailed analysis of 30 guidelines for CAP published around the world and screened with the AGREE instrument…**
- **While guidelines were generally useful, several problems were identified…**
- **Here a few examples…**

Analysis of 30 CAP guidelines with the AGREE Instrument

APPRAISAL OF GUIDELINES
FOR RESEARCH & EVALUATION II

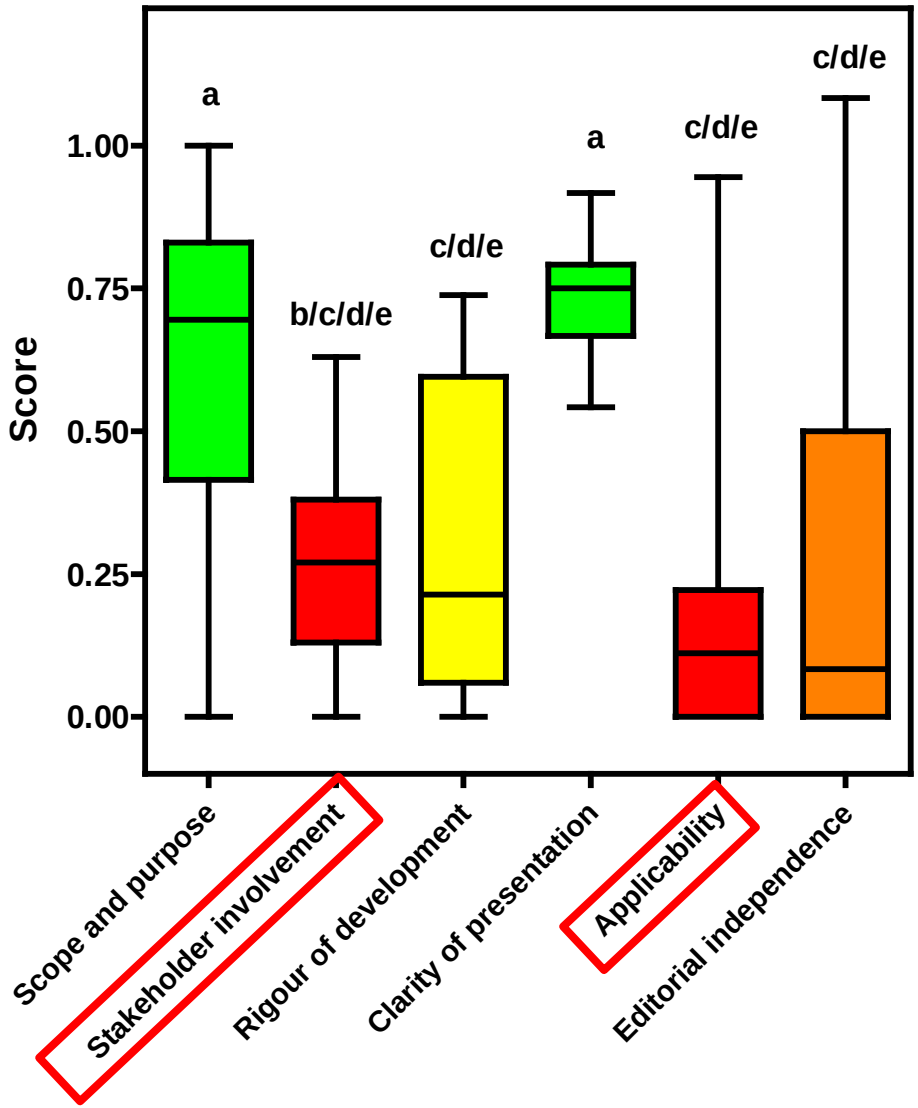
AGREE II

INSTRUMENT

The AGREE Next Steps Consortium

May 2009

http://www.agreetrust.org/



- 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): plots with different letters are significantly different from each other

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 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.**	

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

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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	

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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

But how recent are those guidelines ?

Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

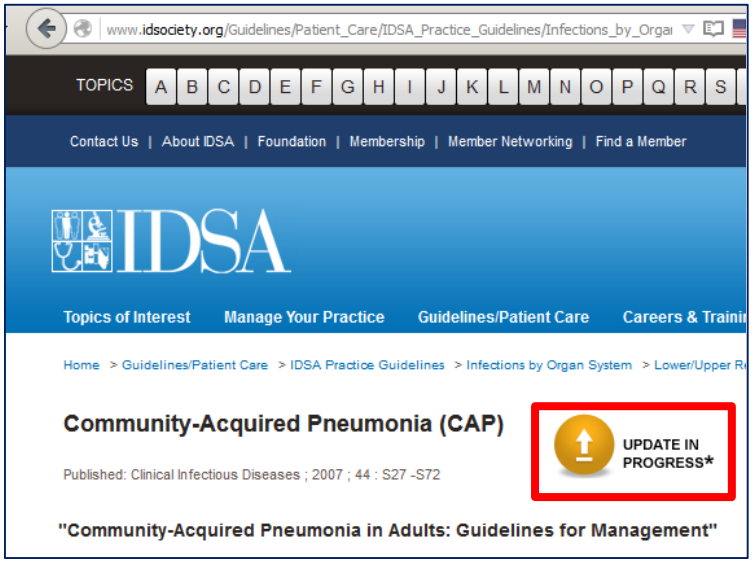
Lionel A. Mandell,[1,a] Richard G. Wunderink,[2,a] Antonio Anzueto,[3,4] John G. Bartlett,[7] G. Douglas Campbell,[8] Nathan C. Dean,[9,10] Scott F. Dowell,[11] Thomas M. File, Jr.[12,13] Daniel M. Musher,[5,6] Michael S. Niederman,[14,15] Antonio Torres,[16] and Cynthia G. Whitney[11]

[1]McMaster University Medical School, Hamilton, Ontario, Canada; [2]Northwestern University Feinberg School of Medicine, Chicago, Illinois; [3]University of Texas Health Science Center and [4]South Texas Veterans Health Care System, San Antonio, and [5]Michael E. DeBakey Veterans Affairs Medical Center and [6]Baylor College of Medicine, Houston, Texas; [7]Johns Hopkins University School of Medicine, Baltimore, Maryland; [8]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Mississippi School of Medicine, Jackson; [9]Division of Pulmonary and Critical Care Medicine, LDS Hospital, and [10]University of Utah, Salt Lake City, Utah; [11]Centers for Disease Control and Prevention, Atlanta, Georgia; [12]Northeastern Ohio Universities College of Medicine, Rootstown, and [13]Summa Health System, Akron, Ohio; [14]State University of New York at Stony Brook, Stony Brook, and [15]Department of Medicine, Winthrop University Hospital, Mineola, New York; and [16]Cap de Servei de Pneumologia i Allèrgia Respiratòria, Institut Clínic del Tòrax, Hospital Clínic de Barcelona, Facultat de Medicina, Universitat de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer, CIBER CB06/06/0028, Barcelona, Spain.

original publication

Clinical Infectious Diseases 2007; 44:S27–72

1058-4838/2007/4405S2-0001$15.00
DOI: 10.1086/511159



http://www.idsociety.org
Last visited: 6 March 2016

and would you more happy with this one ?

2015 - Annotated BTS Guideline for the management of CAP in adults (2009) Summary of recommendations

https://www.brit-thoracic.org.uk/document-library/clinical-information/pneumonia/adult-pneumonia/annotated-bts-cap-guideline-summary-of-recommendations/
Last visited: 5 March 2016

Empirical antibiotic choice for adults treated in the community

81. For patients treated in the community, amoxicillin remains the preferred agent at a dose of 500 mg three times daily.[A+]
82. Either doxycycline [D] or clarithromycin [A−] are appropriate as an alternative choice, and for those patients who are hypersensitive to penicillins.
83. Those with features of moderate or high severity infection should be admitted urgently to hospital. [C]

and would you more happy with this one ?

2015 - Annotated BTS Guideline for the management of CAP in adults (2009) Summary of recommendations

https://www.brit-thoracic.org.uk/document-library/clinical-information/pneumonia/adult-pneumonia/annotated-bts-cap-guideline-summary-of-recommendations/
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Empirical antibiotic choice for adults treated in the community

81. For pa
500 m
82. Either
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83. Those
hospi

Empirical antibiotic choice for adults hospitalised with moderate severity CAP

91. Most patients with moderate severity CAP can be adequately treated with oral antibiotics. [C]
92. Oral therapy with amoxicillin and a macrolide is preferred for patients with moderate severity CAP who require hospital admission. [D]
93. When oral therapy is contraindicated, the preferred parenteral choices include intravenous amoxicillin or benzylpenicillin, together with clarithromycin. [D]
94. For those intolerant of penicillins or macrolides, oral doxycyline is the main alternative agent. Oral levofloxacin and oral moxifloxacin are other alternative choices. [D]
95. When oral therapy is contraindicated in those intolerant of penicillins, recommended parenteral choices include levofloxacin monotherapy or a second-generation (eg, cefuroxime) or third-generation (eg, cefotaxime or ceftriaxone) cephalosporin together with clarithromycin. [D]

What do we need to do (in 4 steps)?

1. **Know you epidemiology**
   → aim at the bug

2. **Know your patient**
   → what is her/his environment
   → how will you administer the drug (route, dose, schedule)

3. **What is the risk /benefit ratio ?**
   → expected therapy
   → toxicities to avoid

4. **What is the quality of the drug prescribed ?**
   → is cheaper (always) the best?

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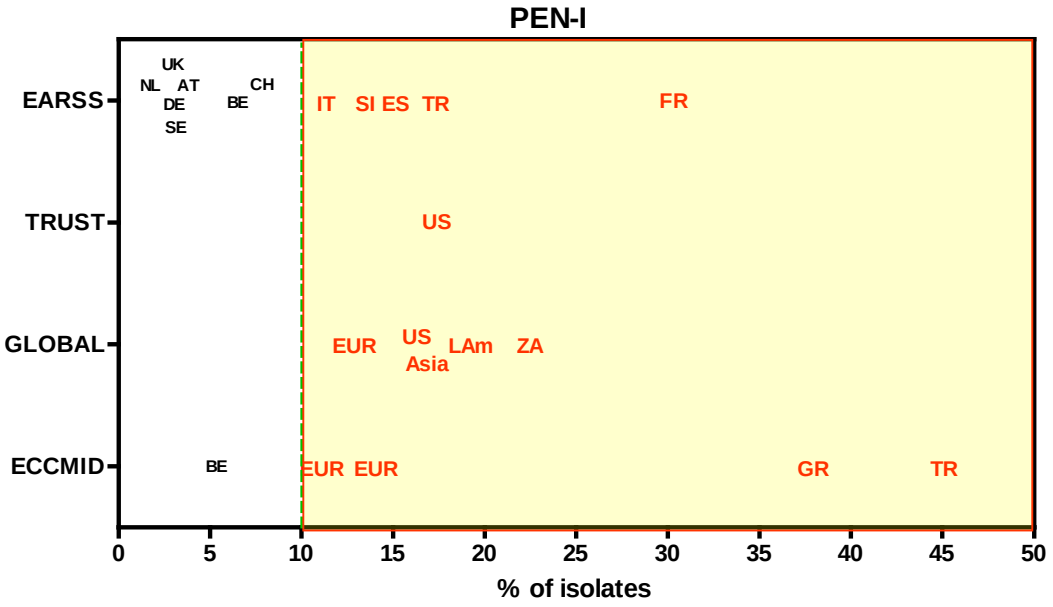
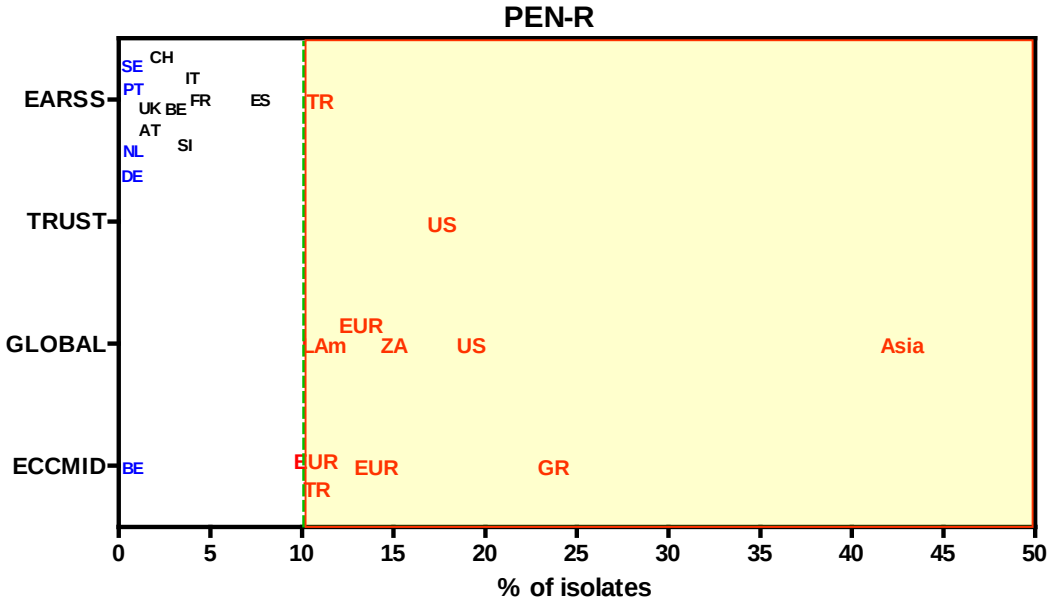
Resistance of *S. pneumoniae* * to penicillin as presented in 2011

*Analysis of resistance to penicillins (with CAP as main indication) in surveillance systems or publications (*S. pneumoniae*)

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





Carbonnelle *et al.*, in preparation

Resistance of *S. pneumoniae* * to macrolides and tetracyclines as presented in 2011

*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
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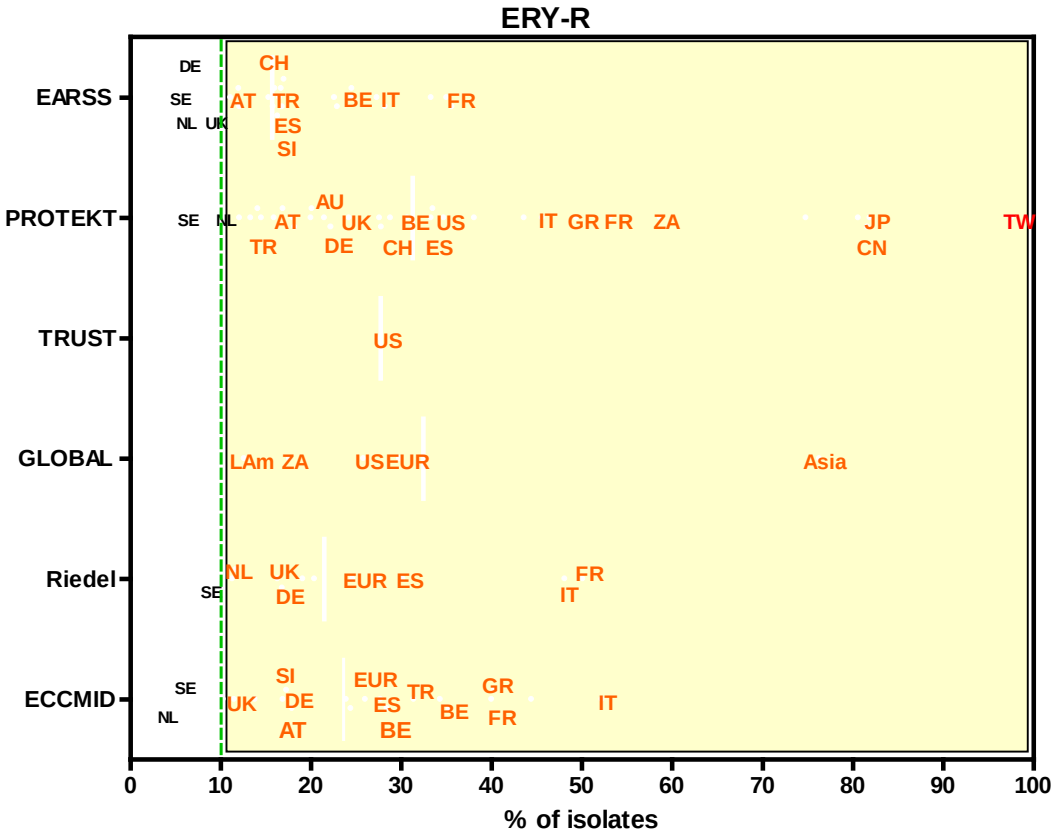
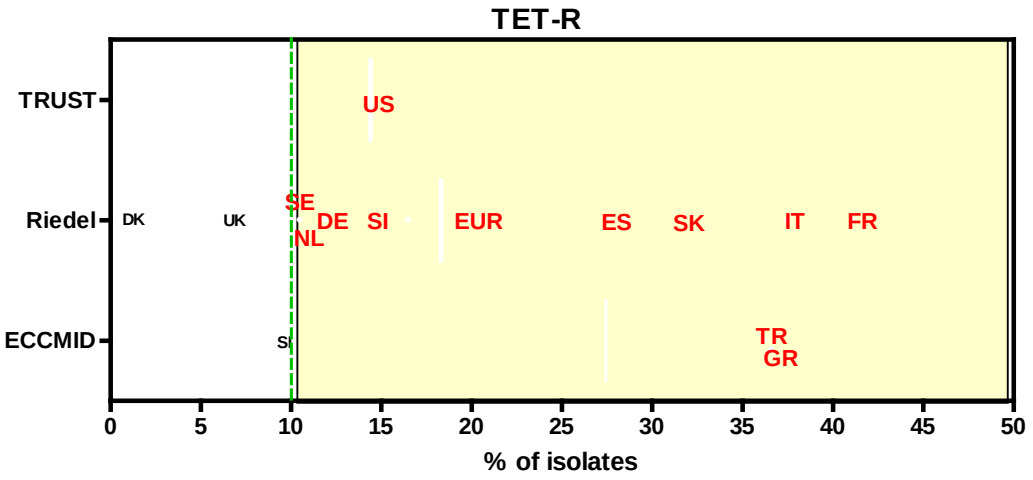
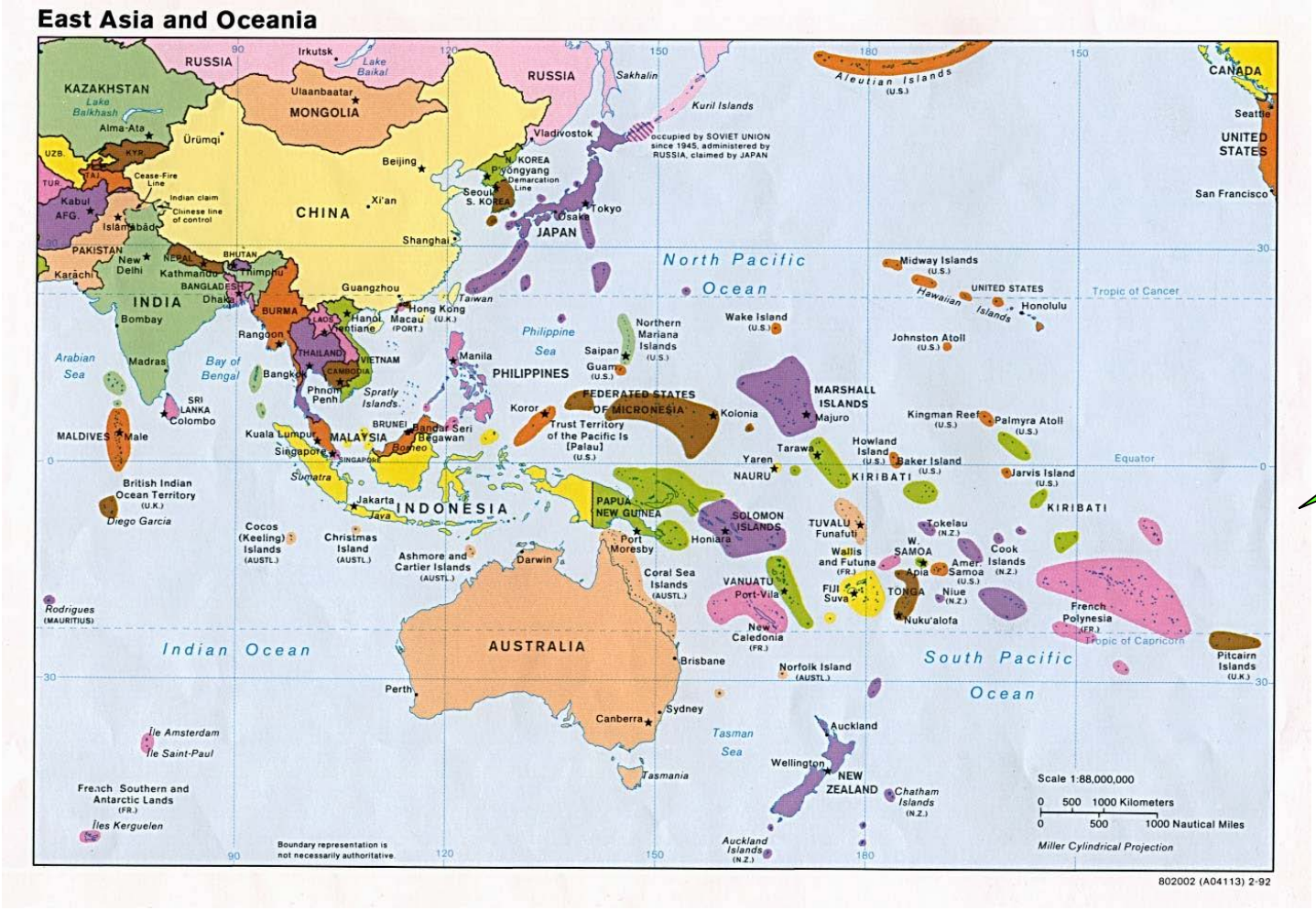




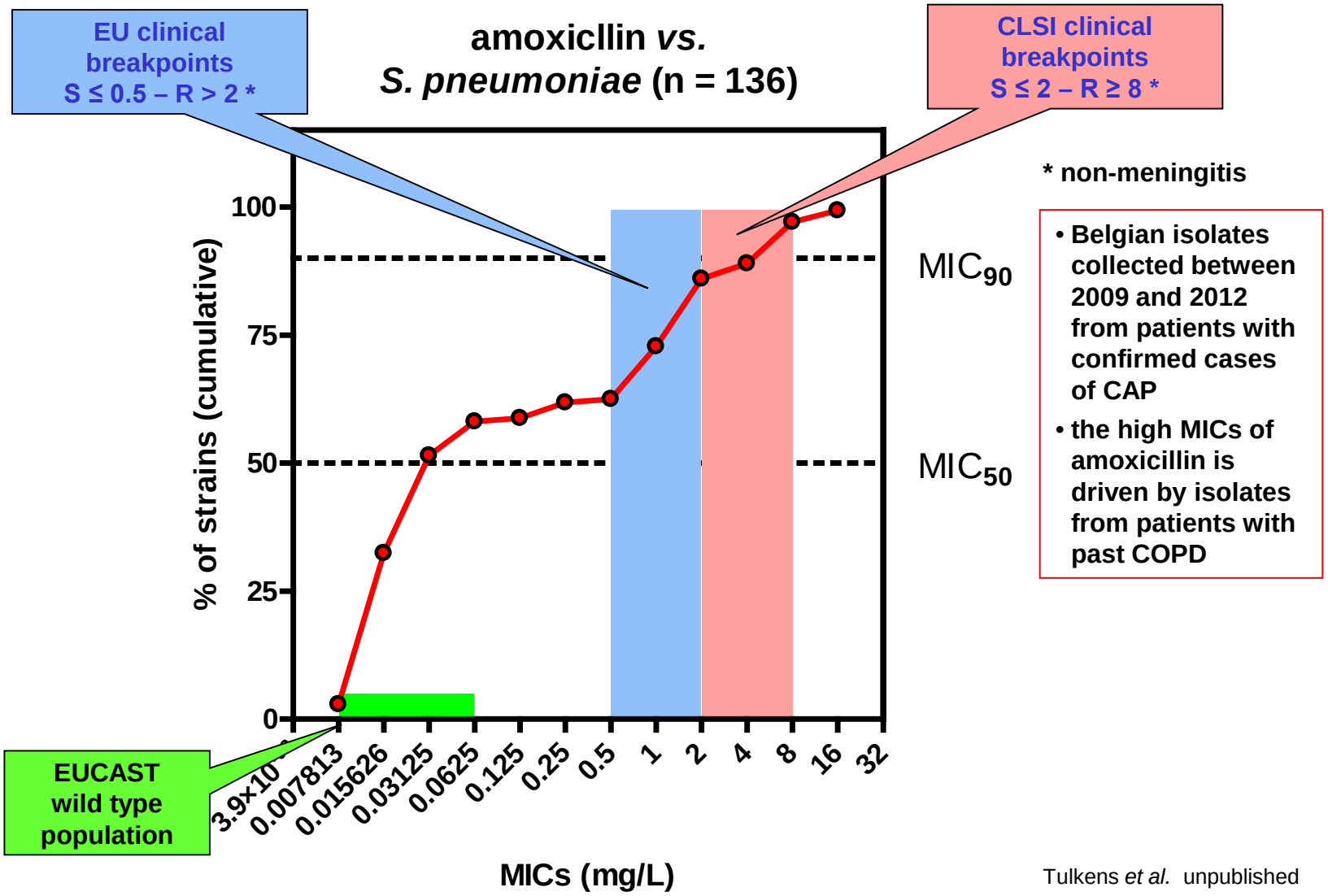
The message: make and use surveillance studies

Countries should know THEIR resistance patterns !



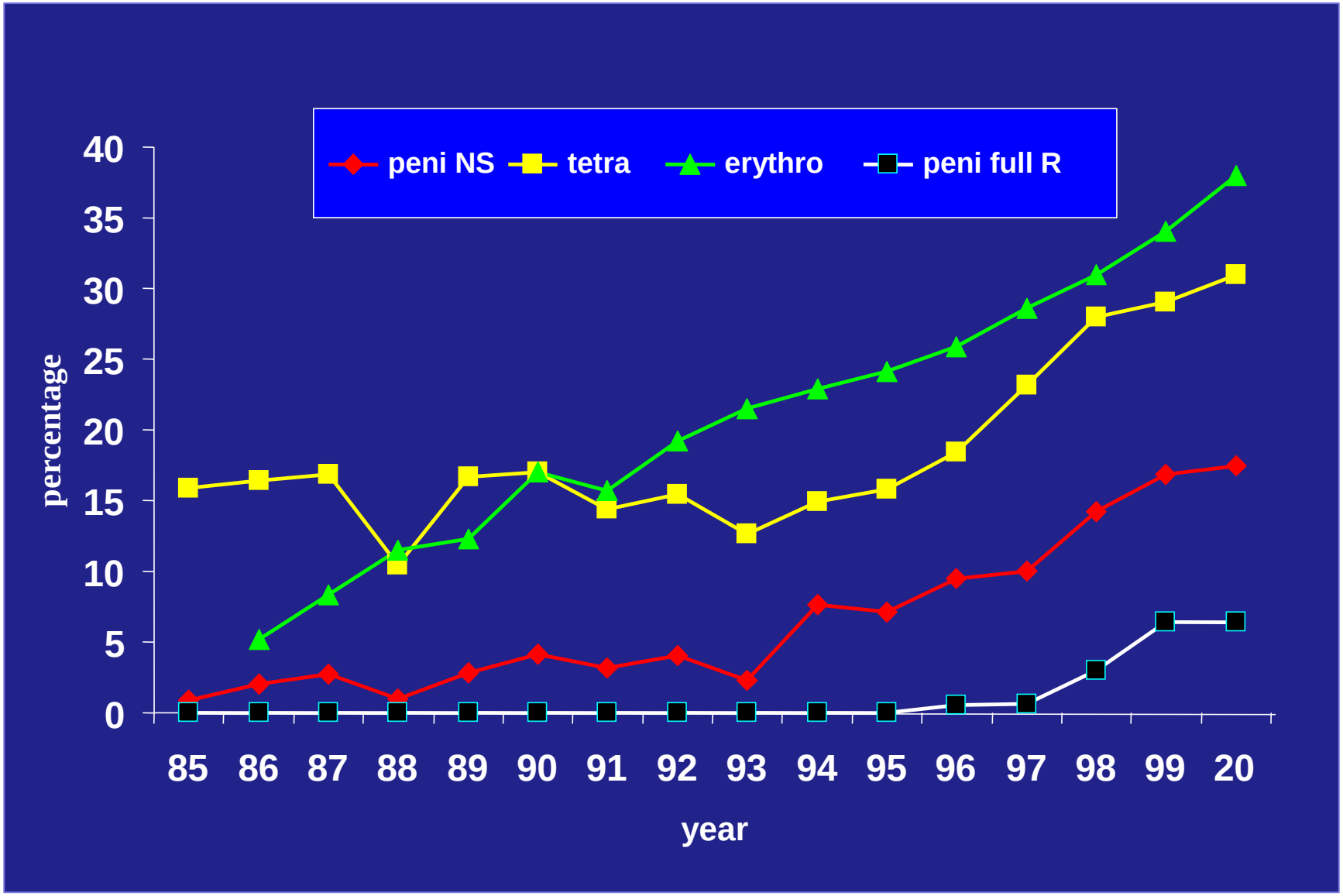
Where are YOU ?

Know which breakpoints you use !

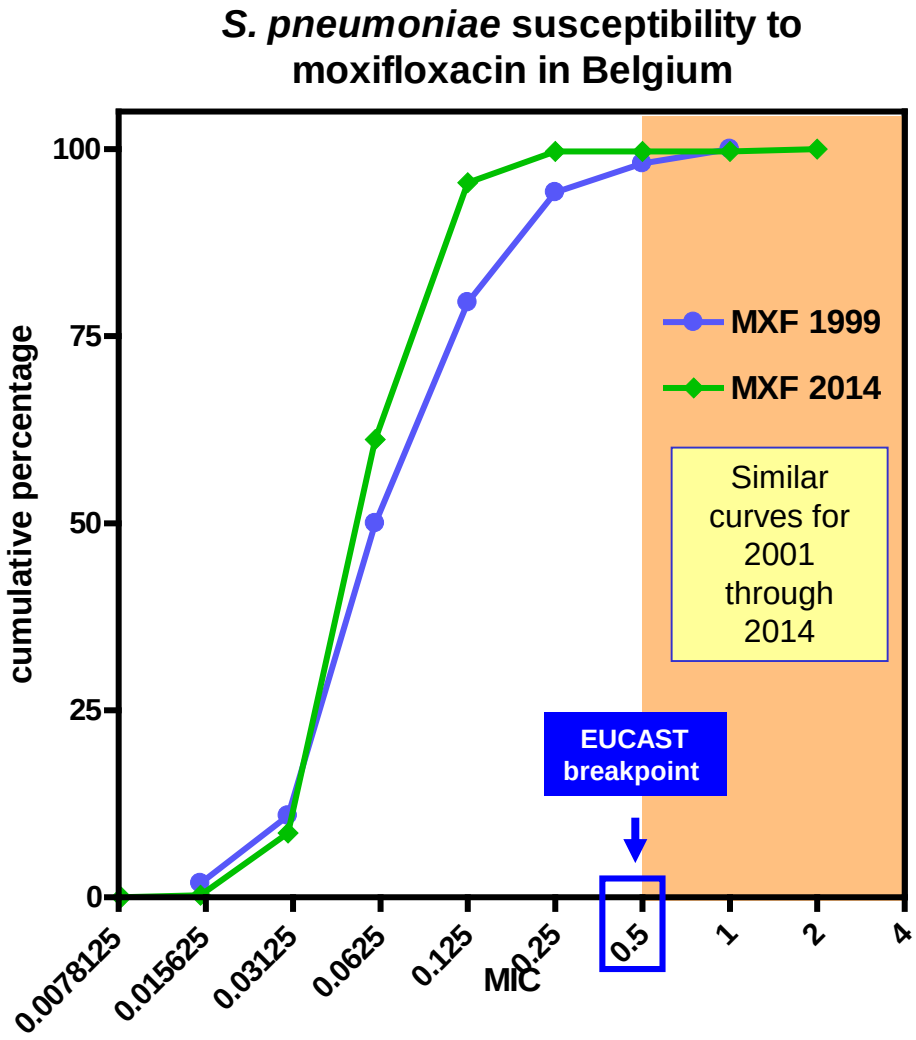


Tulkens *et al.* unpublished

Know where is the risk of emergence of resistance ?
S. pneumoniae in Belgium from 1985 to 2000 …



Know where is the risk of emergence of resistance ?
S. pneumoniae in Belgium from 1999 to 2014 for moxifloxacin



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

- Non invasive respiratory tract infections
- similar results in 2008 for a collection of *S.pneumoniae* from clinically-confirmed CAP (n=132)

- Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 312 in 2014)
- Data available yearly for 1999 through 2014
- http://www.iph.fgov.be

Vanhoof *et al*. 19th ECCMID, Helsinki, 2009
Ceyssens *et al*. 35th RICAI, Paris, 2015
Ceyssens *et al.* submitted

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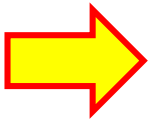
   → is cheaper (always) the best?

The environment means the bacteria and the resistance but also how you will administer the drug

- Questions to ask for the bacteria:
  - do I need to cover for Gram-negative
    → **enlarging the spectrum ?**
  - and the so-called "a-typicals"
    → **adding a macrolide or using a fluoroquinolone ?**

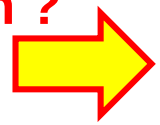


talk to your microbiologist(s)… and the drug specialist(s)

The environment means the bacteria and the resistance but also how you will administer the drug

- Questions to ask for the bacteria:
  - do I need to cover for Gram-negative
    → enlarging the spectrum
  - and the so-called "a-typicals"
    → adding a macrolide of using
    a fluoroquinolone

- Question for the patient: can I treat her/him as needed
  - **how many times a day for a beta-lactam ?**
  - **what is the dose of a macrolide ?**
  - **may I use a fluoroquinolone once-daily ?**



a bit of PK/PD

PK/PD in a nutshell…

- β-lactams are "time-dependent" and MUST remain above the MIC as long as possible…

  ➔ a large peak (large dose) is useless…

  ➔ **give them many times a day (3-4 times)**

do not forget the night …

or even use the 4h infusion (doripenem*, meropenem…)

… or the 24h infusion (ceftazidime*, piperacillin/tazobactam

* approved modes of administration

PK/PD in a nutshell…

- β-lactams are "time-dependent" and MUST remain above the MIC as long as possible…
  - ➔ a large peak (large dose) is useless…
  - ➔ **give them many times a day (3-4 times)**

- Macrolides, oxazolidinones, vancomycin, tigecyline are all AUC-dependent drugs
  - ➔ **the total daily dosage is critical**

AUC_{24h} = daily dose / Clearance

PK/PD in a nutshell…

- β-lactams are "time-dependent" and MUST remain above the MIC as long as possible…
  - ➔ a large peak (large dose) is useless…
  - ➔ **give them many times a day (3-4 times)**
- Macrolides are AUC-dependent drugs
  - ➔ **the total daily dosage is critical**
- Fluroquinolones are both C_{max}- and AUC-dependent
  - ➔ **levofloxacin may need 2 x 500 mg** (750 mg qD in the US)
  - ➔ **moxifloxacin 400 mg qD provides both a peak* and an AUC ****

*** C_{max}/MIC > 10**
**** AUC/MIC > 100**

Aminoglycosides are C_{max}-dependent (see later in this meeting)

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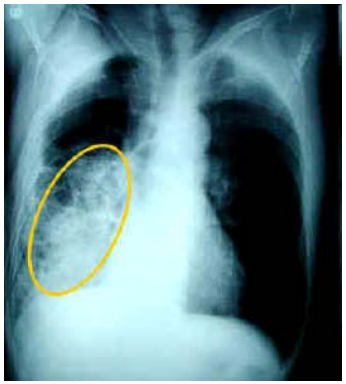
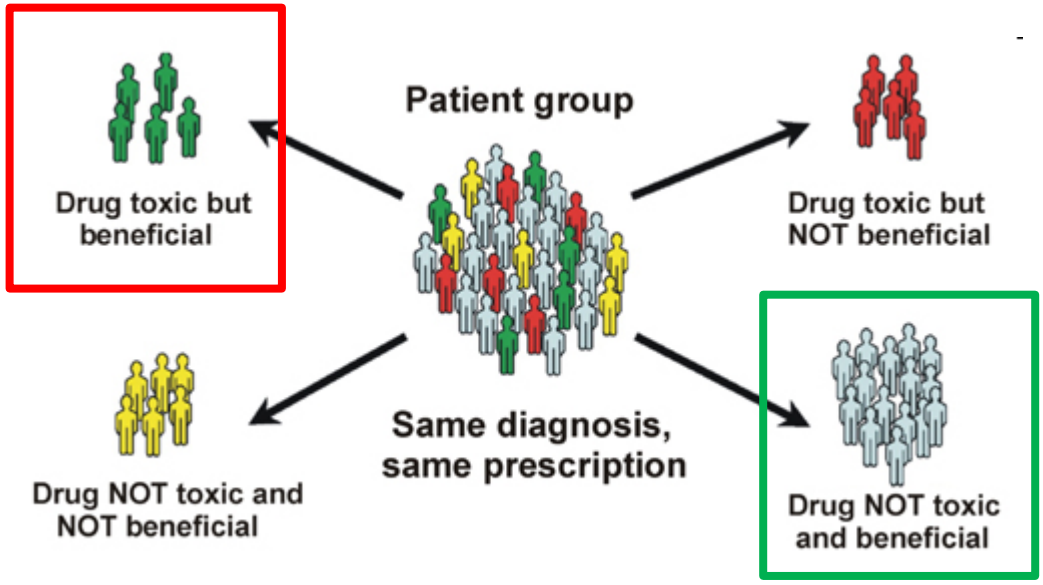
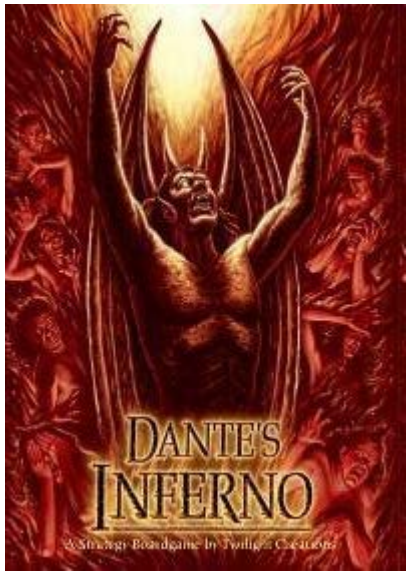
Therapy and side effects…



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)

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 myasthenia • **QTc prolongation** • **Drug interactions (CYP450)** • Digestive tract: diarrhoea, nausea, vomiting, dysgueusia • CNS: headache, dizziness

severely limited

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

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)

**** based on the current SmPC including the 2012 EMA warning for levofloxacin**

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.

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 main point will be a correct evaluation of the benefit / risk ratio in the **specific environment** and for the **specific patient**

Do not say that …

What do we need to do (in 4 steps)?

1. **Know you epidemiology**
   → aim at the bug

2. **Know your patient**
   → what is her/his environment
   → how will you administer the drug (route, dose, schedule)

3. **What is the risk /benefit ratio ?**
   → expected therapy
   → toxicities to avoid

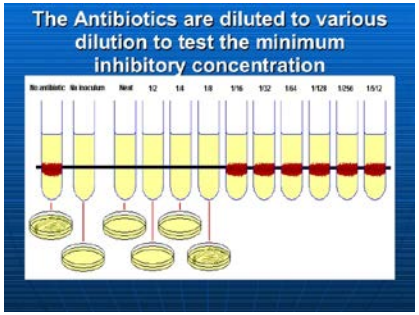
4. **What is the quality of the drug prescribed ?**
   → is cheaper (always) the best?

I discussed this at length at the previous RTI…
I'll briefly comment here…

A number of problems… and questions…

Questions for the prescriber…

- **what is the true drug content ?**
  - **MICs and risk of emergence of resistance ?**



http://image.slidesharecdn.com/antibiotic-sensitivity-testing-1225252356931501-9/95/antibiotic-sensitivity-testing-37-728.jpg?cb=1323826773
Last visited: 11 March 2016

- **what is the therapeutic equivalence ?**
  - **animal models and clinical experience of efficacy and safety**

- **what is the pharmaceutical quality ? (biophysical forms and impurities)**
  - **toxicity and other intolerances**

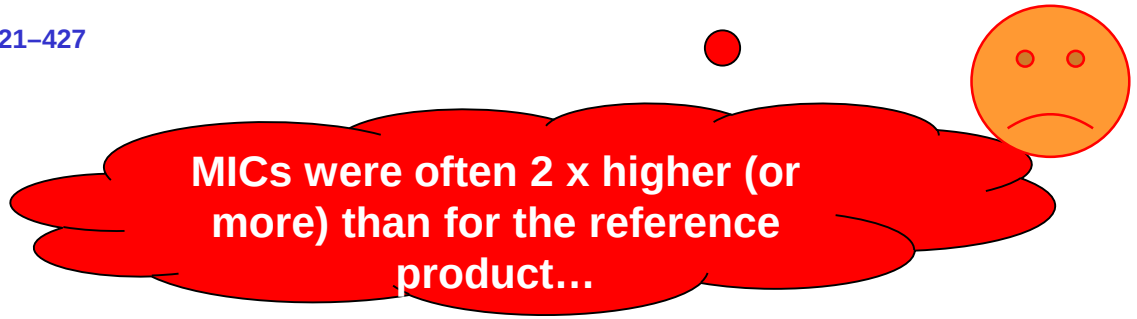
True drug content ?

Table 1 Comparison of antimicrobial activity against various clinical isolates in a brand name and generic antibiotics

Antibiotic	Pathogen (no.)	No. of generic markers	Nonidentical rate of the MIC value of all generics (mean ± SD)	MIC distribution (%) of the most different generic versus brand name drug						
				1/8	1/4	1/2	1[a]	2	4	8
Vancomycin	MRSA (90)	5	25.00 ± 15.52	–	–	–	54.4	45.6	–	–
Teicoplanin	MRSA (147)	7	28.09 ± 10.29	–	–	–	59.2	40.1	0.7	–
Cefotiam	*Staphylococcus aureus* (100)	7	8.71 ± 3.04	–	–	–	87.0	13.0	–	–
	Escherichia coli (100)	7	12.00 ± 5.89	–	–	–	77.0	22.0	1.0	–
Ceftriaxone	*Streptococcus pneumoniae* (126)	6	12.70 ± 4.77	–	–	–	81.7	18.3	–	–
Ceftazidime	*Pseudomonas aeruginosa* (100)	2	3.00 ± 2.83	–	–	–	95.0	5.0	–	–
Meropenem	*P. aeruginosa* (100)	7	18.57 ± 3.46	–	–	–	78.0	19.0	2.0	1.0
Imipenem	*P. aeruginosa* (100)	4	9.00 ± 2.58	–	–	–	88.0	11.0	1.0	–

MRSA methicillin-resistant *Staphylococcus aureus*[a]Note that the distribution of one minimal inhibitory concentration (1 MIC) shows the identical rate with the brand drug: MIC was determined by broth micro-dilution method using powder in each drug vial

Fujimura & Watanabe J Infect Chemother (2012) 18:421–427



A number of problems… and questions…

Questions for the prescriber…

- what is the true drug content ?
  - MICs and risk of emergence of resistance ?

http://www.gaebler.com/How-to-Start-a-Laboratory-Animals-Business.htm
Last accessed: 11 March 2016

- **what is the therapeutic equivalence ?**
  - **animal models and clinical experience of efficacy and safety**

http://www.buzzle.com/articles/staph-infections-staph-infection-treatment-and-symptoms.html
Last visited: 25 March 2014 (no longer available)

- what is the pharmaceutical quality ? (biophysical forms and impurities)
  - toxicity and other intolerances

Variable efficacy in a well accepted PK/PD animal model …

Vancomycin in the neutropenic mouse thigh infection model

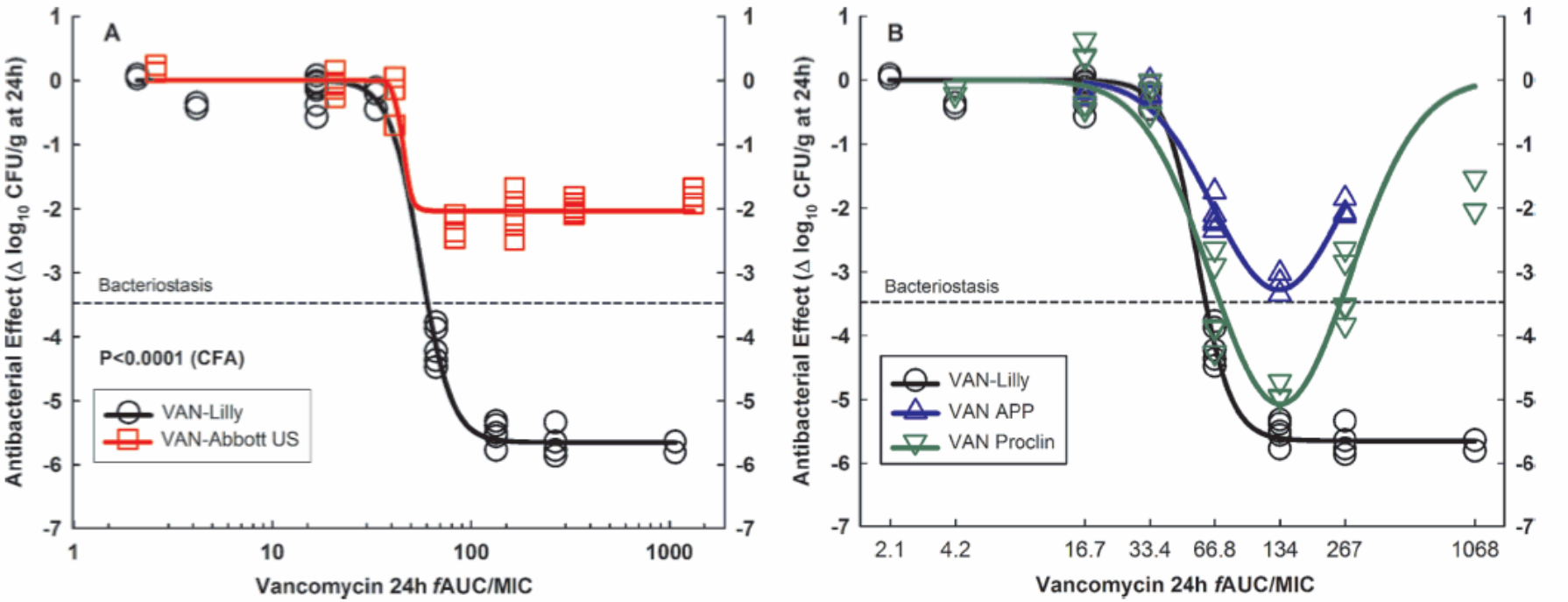


FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per day) using the neutropenic mouse thigh infection model (each data point represents the mean CFU/g of both thighs from a single mouse). (A) Pharmacodynamic patterns of VAN-Abbott US and VAN-Lilly fitted to the Hill model. Despite containing a significantly greater concentration of API (125%), VAN-Abbott US was completely ineffective *in vivo*. VAN-Abbott US is shown in a separate graph because of its greater AUC/MIC ratio than that of VAN-Lilly (123%; their dosing regimens were identical). (B) VAN-APP and VAN-Proclin were both pharmaceutically equivalent to VAN-Lilly, but neither was therapeutically equivalent due to their marked Eagle effect. The curve for VAN-APP ends at 300 mg/kg (*f*AUC/MIC, 267 h) because this product was discontinued and the remaining amount was insufficient for the highest doses.

Vesga *et al.* Antimicrob Agents Chemother. 2010; 54:3271–3279.

Clinical alerts (efficacy and safety) ?

Safety and efficacy of generic drugs with respect to brand formulation

Luca Gallelli[1], Caterina Palleria[1], Antonio De Vuono[2], Laura Mumoli[1], Piero Vasapollo[2], Brunella Piro[3], Emilio Russo[1]

[1]Department of Health Science, Regional Center on drug information, Mater Domini University Hospital, Italy and Chair of Pharmacology, School of Medicine, University of Catanzaro, [2]Department of General Medicine, ASP Cosenza, [3]Department of Pharmacovigilance, ASP Cosenza, Italy

J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1):S110-4.

"In this case-review, we report the lack of efficacy during treatment with generic formulations of fluoroquinolones and discuss the relative reasons also considering the limitations of this legal approach."

Clinical alerts (efficacy and safety) ?

Safety and efficacy of generi to brand formulation

Luca Gallelli[1], Caterina Palleria[1], Antonio De Vuono[2], L Emilio Russo[1]

[1]Department of Health Science, Regional Center on drug information, Ma School of Medicine, University of Catanzaro, [2]Department of General Mec Cosenza, Italy

J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1

In this case-review, w treatment with generi and discuss the rela limitations

CONCLUSION

In conclusion, the use of generic drugs could be related with an increased days of disease (time to relapse) or might lead to a therapeutic failure; on the other hand, a higher drug concentration might expose patients to an increased risk of dose-dependent side-effects. Overall, it is advisable to well evaluate the effects of generic formulations during the therapeutic treatment.

In agreement with Manning and Smith,[41] it is necessary to underline the importance that clinician's change their attitude toward pharmacovigilance and post-marketing surveillance systems, which can help to identify the lack of efficacy during the treatment with generic formulations.

ACKNOWLEDGMENTS

The Italian Drug Agency (Agenzia Italiana del Farmaco) is kindly acknowledged for its financial and technical support.

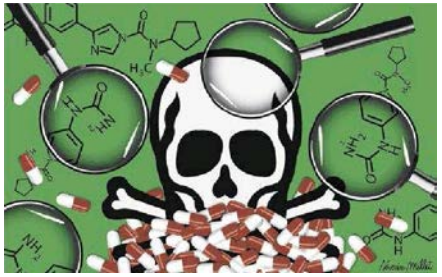
A number of problems… and questions…

Questions for the prescriber…

- what is the true drug content ?
  - MICs and risk of emergence of resistance ?

- what is the therapeutic equivalence ?
  - animal models and clinical experience of efficacy and safety

- **what is the pharmaceutical quality ? (biophysical forms and impurities)**
  - **risk of toxicity and other intolerances**



Le Monde – 9 mars 2016
http://www.lemonde.fr/journalelectronique/donnees/protege/20160309/Le_Monde_20160309.zip
Last visited: 11 March 2016

Impurities in generic ciprofloxacin…

Available online at www.sciencedirect.com
ScienceDirect
Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 743–754
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Generic ciprofloxacin tablets contain the stated amount of drug and different impurity profiles: A ^{19}F, ^{1}H and DOSY NMR analysis

Saleh Trefi, Véronique Gilard, Myriam Malet-Martino*, Robert Martino

Groupe de RMN Biomédicale, Laboratoire SPCMIB (UMR CNRS 5068), Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse cedex, France

Received 29 November 2006; received in revised form 19 February 2007; accepted 19 February 2007
Available online 1 March 2007

Abstract

The objective of this study was to control the purity of 16 commercial formulations of ciprofloxacin tablets purchased in different countries or via the Internet using ^{19}F and ^{1}H nuclear magnetic resonance (NMR). Twelve out of the sixteen commercial formulations of ciprofloxacin measured by ^{19}F NMR contain the active ingredient within $100 \pm 5\%$ of stated concentration. Three formulations have a lower ciprofloxacin content between 90 and 95% and one shows a higher concentration superior to 105%. The impurity profile was characterised using ^{19}F and ^{1}H NMR, and is characteristic of the manufacturer. Four to twelve fluorinated impurities among them fluoride ion and two already known compounds were detected and quantified in the sixteen formulations analysed by ^{19}F NMR. Two other non-fluorinated impurities were observed in the seven formulations analysed with ^{1}H NMR. The total content of impurities as well as their individual levels are in agreement with those reported previously in the few studies devoted to ciprofloxacin purity. However, all the formulations do not comply with the limits for impurities given in the ciprofloxacin monograph of the European Pharmacopeia. Finally, a "signature" of the formulations was obtained with Diffusion-Ordered SpectroscopY (DOSY) ^{1}H NMR which allowed the characterisation of some excipients present in the formulations studied.

Keywords: ^{19}F NMR; ^{1}H NMR; DOSY ^{1}H NMR; Ciprofloxacin; Impurities

Impurities in generic ciprofloxacin…

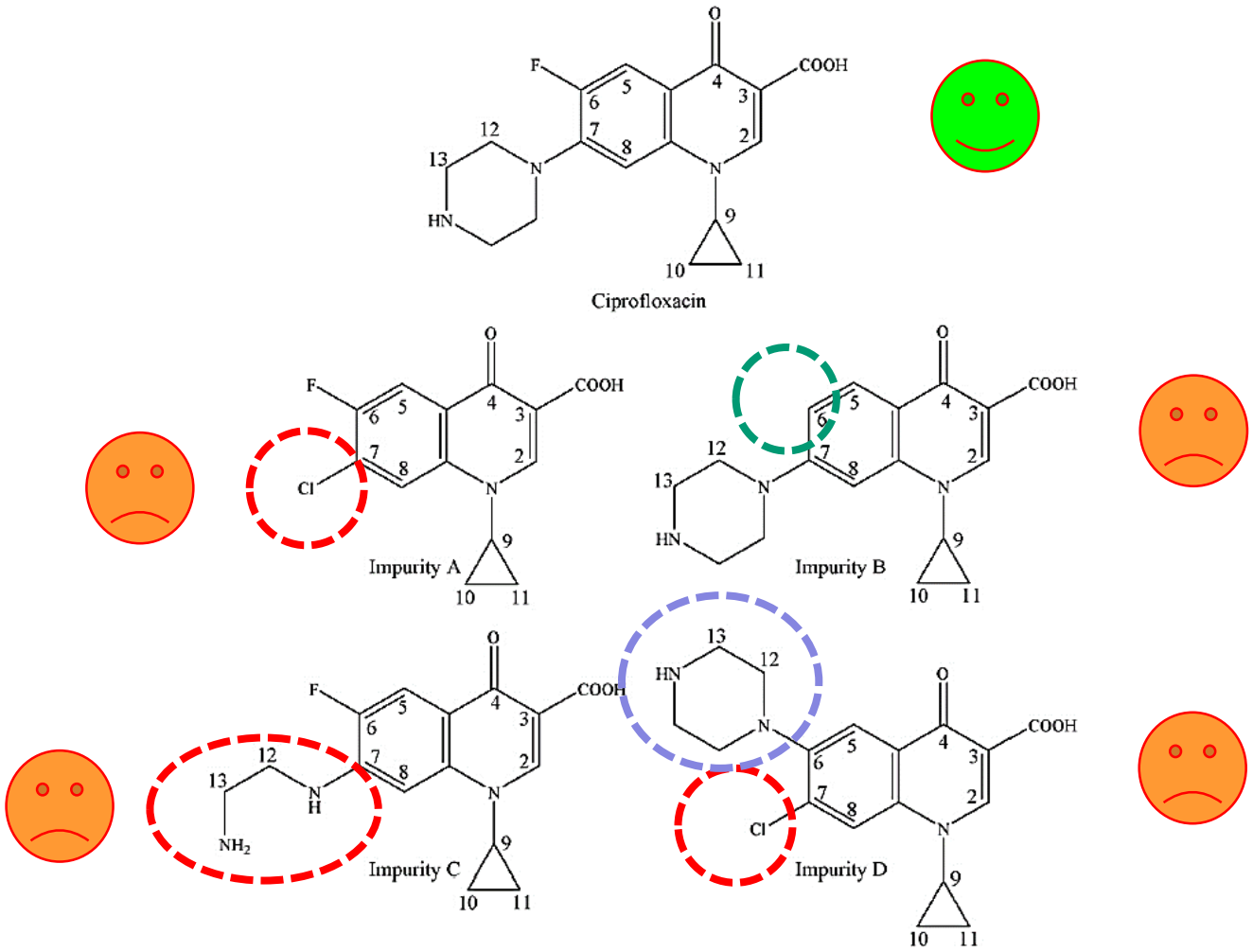
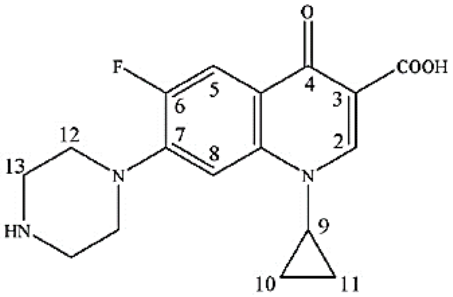


Fig. 1. Structure of ciprofloxacin and its main impurities.

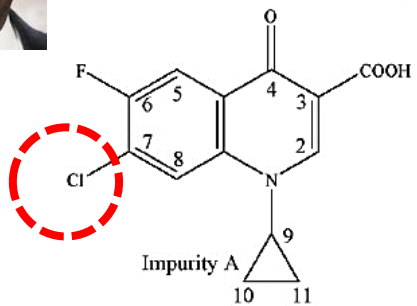
Trefi *et al.* Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 743–754

Impurities in generic ciprofloxacin…

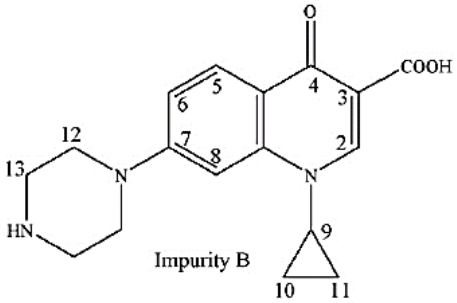
I's a synthesis precursor, guys !



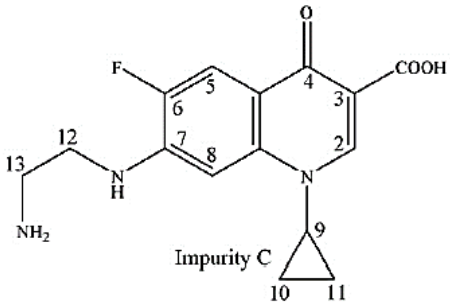
Ciprofloxacin



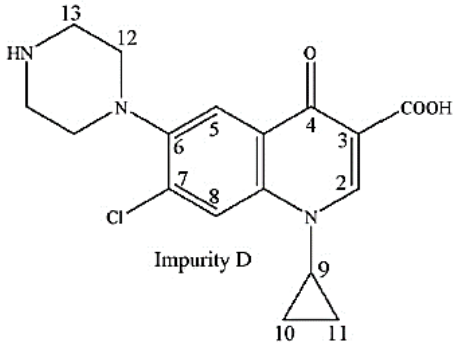
Impurity A



Impurity B



Impurity C



Impurity D

what on earth is this one ?

Fig. 1. Structure of ciprofloxacin and its main impurities.

Trefi *et al.* Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 743–754

A number of problems… and questions * …

Questions for the authorities

no time to address them in details now, but ask questions…

- **which are the (effective) controls ?**
  - **how many and how frequent are such controls in your country ?**
- **risk of overuse**
  - **cheap is cheap → how do you prevent overuse ?**
- **what about the future ?**
  - **will "low cost suppliers" pay for future developments**
  - **do YOU have a plan for future antibacterial agents ?**

Conclusions (and food for thought)

- Choosing the right antibiotic (and its right supplier) is an difficult task but **cannot be neglected** and left to technocrats…
- The choice must be balanced between the apparently contradictory requirements of **efficacy**, **toxicity**, and **cost**
- A rational approach is possible, where
  - **efficacy in your environment** comes first
  - **side effects** are **controllable** (but quality must be controlled !)
  - **costs** are expressed in relation to **utility** (for the patient and the society) *
- At the end of the day, **it will always be the doctor's choice**, but that choice MUST be rational and based on best evidence applied to the patient, with due respect to the community…

---

* not addressed here but ask question (I'm a governor of DRIVE AB … to renew the economical framework of antibiotics)

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 <u>medical</u> 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