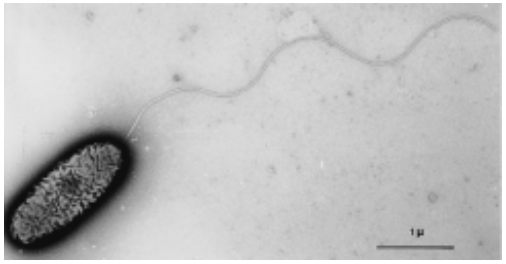
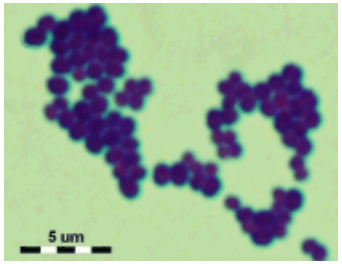
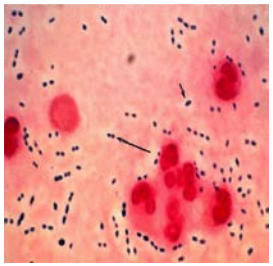
Three WHO Priority Pathogens:

P. aeruginosa (critical), *S. aureus* (high), *S. pneumoniae* (medium)







Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology & Center for Clinical Pharmacy

Louvain Drug Research Institute,

Université catholique de Louvain

Brussels, Belgium

Middle East Anti-Infectives Forum
Yas Island, Abu Dhabi, U.A.E
10-11 November 2017

With approval of the Belgian Common Ethical Health Platform – visa no. 17/V1/10411/093945

Disclosures and slides availability

- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica, Debiopharm
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), Walloon and Brussels Regions, European Union (*FP7 programme*)

- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

- Decision-making and consultation bodies
  - European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
  - European Medicines Agency (external ad-hoc expert)
  - US National Institutes of Health (grant reviewing)
  - Drive-AB [*Driving reinvestment in R&D and responsible use for antibiotics*] (governance)

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

WHO priority list of antibiotic resistant bacteria …

World Health Organization

GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

Chair: E. Tacconelli (Infectious Diseases, DZIF Center, Tübingen University, Germany) and N. Magrini (WHO, EMP Department)

Coordinating group: Y. Carmeli, Tel Aviv University, Israel; S. Harbarth, University of Geneva, Switzerland; G. Kahlmeter, University of Uppsala, Sweden; J. Kluytmans, University Medical Center Utrecht, Netherlands; M. Mendelson, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa; C. Pulcini, University of Lorraine and Nancy University Hospital, France; N. Singh, George Washington University, USA; U. Theuretzbacher, Center for Anti-infective Agents, Austria

http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/
Published: 27 Feb 2017; Last accessed: 21 Oct 2017

WHO priority list of antibiotic resistant bacteria: Methodology (in short) …

- 8 experts (infectious diseases, clinical microbiology, R&D, public health and infection control)
- Multi-criteria decision analysis (MCDA) technique using both expert opinion and evidence-based data
- Prioritization through:
  1. Selection of antibiotic-resistant bacteria to be prioritized;
  2. Selection of criteria for prioritization;
  3. Data extraction and synthesis;
  4. Scoring of alternatives and weighting of criteria by experts; and
  5. Finalization of the ranking of pathogens.
- Criteria:
  - all-cause mortality,
  - healthcare and community burden,
  - prevalence of resistance,
  - 10-year trend of resistance,
  - transmissibility,
  - preventability in hospital and community settings,
  - treatability
  - current pipeline.

http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/
Published: 27 Feb 2017; Last accessed: 21 Oct 2017

WHO priority list of antibiotic resistant bacteria: the proposals (in short) …

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-res fluoroquinolone-resistant

Priority 3: MEDIUM

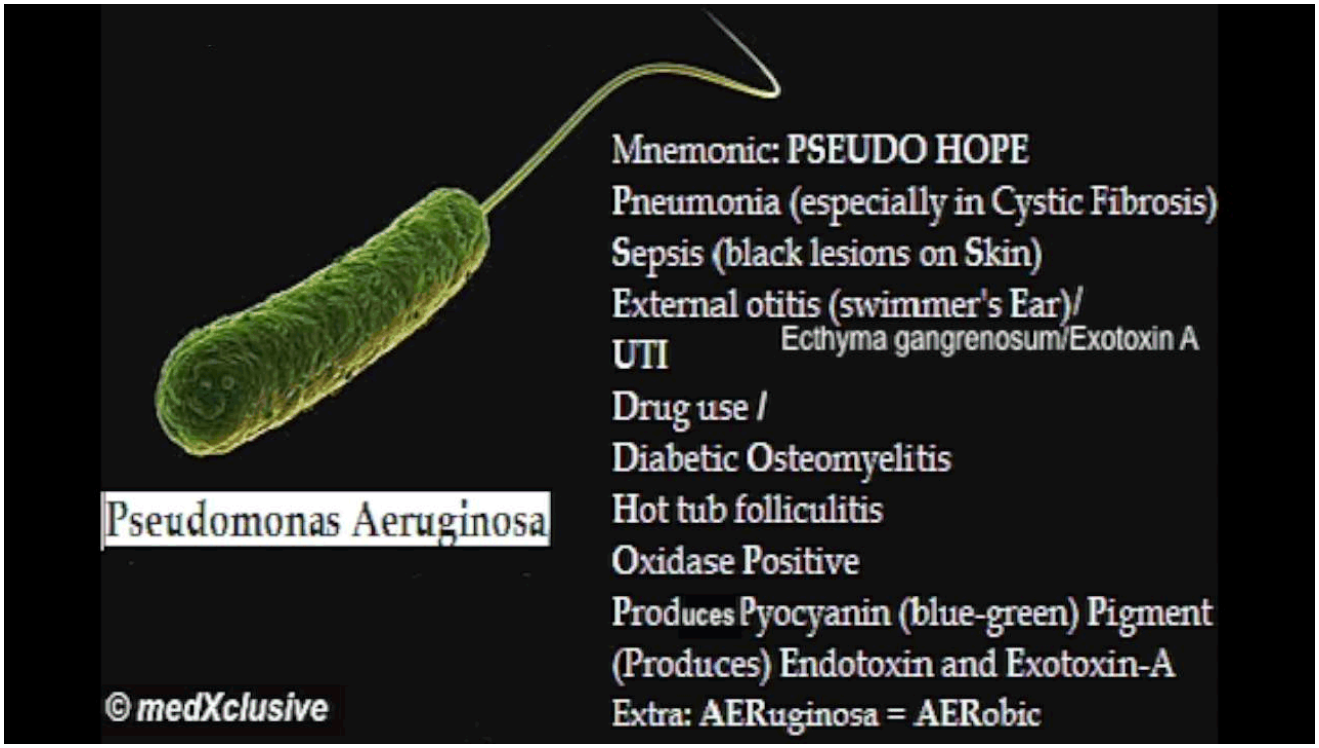
Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant

http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/
Published: 27 Feb 2017; Last accessed: 21 Oct 2017

Pseudmonas aeruginosa



https://www.youtube.com/watch?v=8E3_e1TWac4
Last accessed: 21 Oct 2017

Pseudmonas aeruginosa

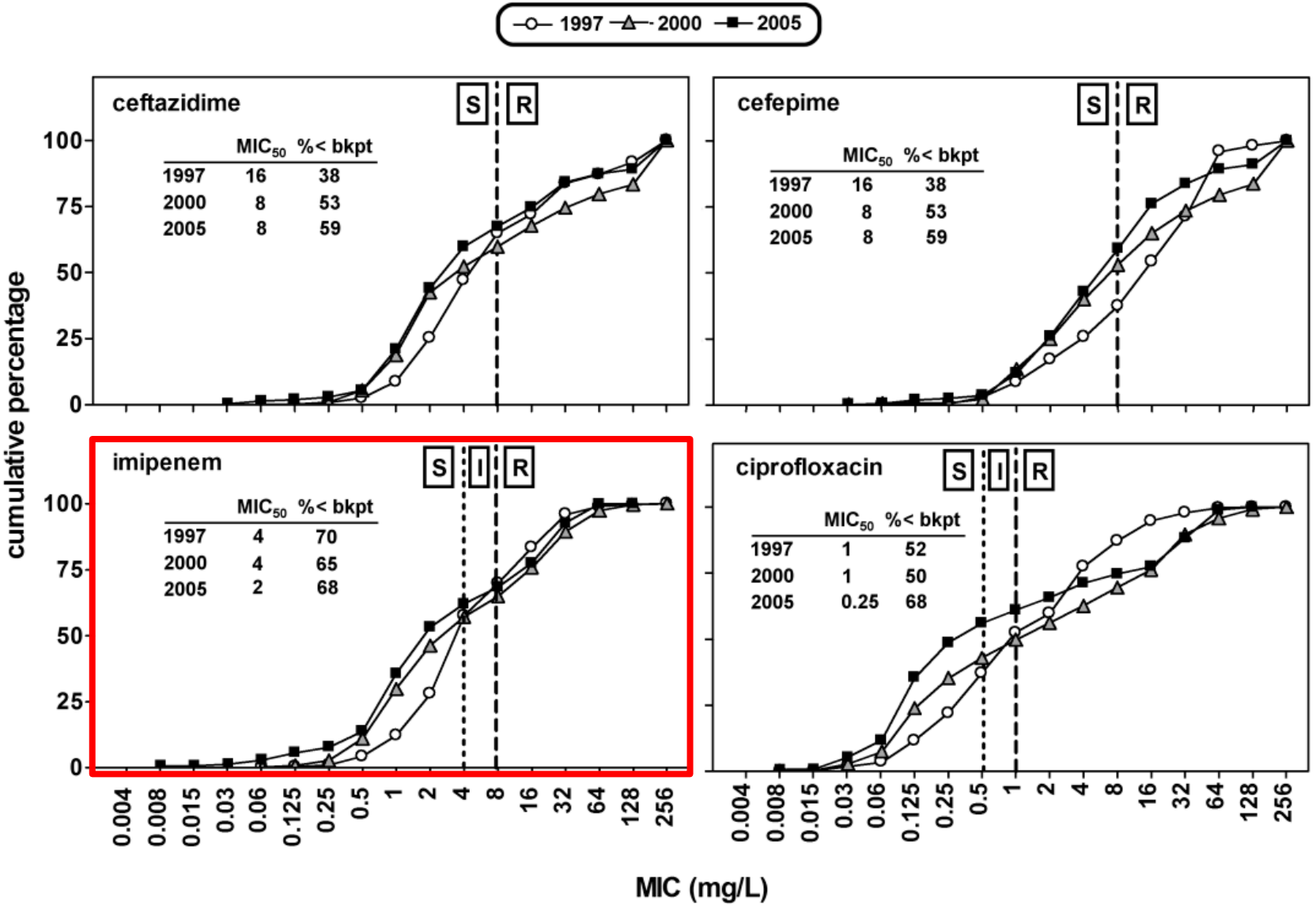
https://www.youtube.com/watch?v=8E3_e1TWa
Last accessed: 21 Oct 2017

Key points for this lecture:

- **ubiquitous** organism, widely distributed in nature.[1]
- most prevalent aerobic non-fermenter Gram-negative bacteria identified as the causative pathogen in **nosocomial infections**.[2]
- through high genomic plasticity, it can survive in a wide range of environmental habitats (reservoirs)[3] including **medical devices** (with long-term transmission).
- intrinsically **resistant to many antibiotics** (double membrane and efflux), limiting potential therapies to carboxy- and ureido-penicillins, groupe 3-5 cephalosporins, carbapenems, monobactams, aminoglycosides, fluoroquinolones, polymyxins.[2]
- BUT **has developed mechanisms of resistance** to all of these !

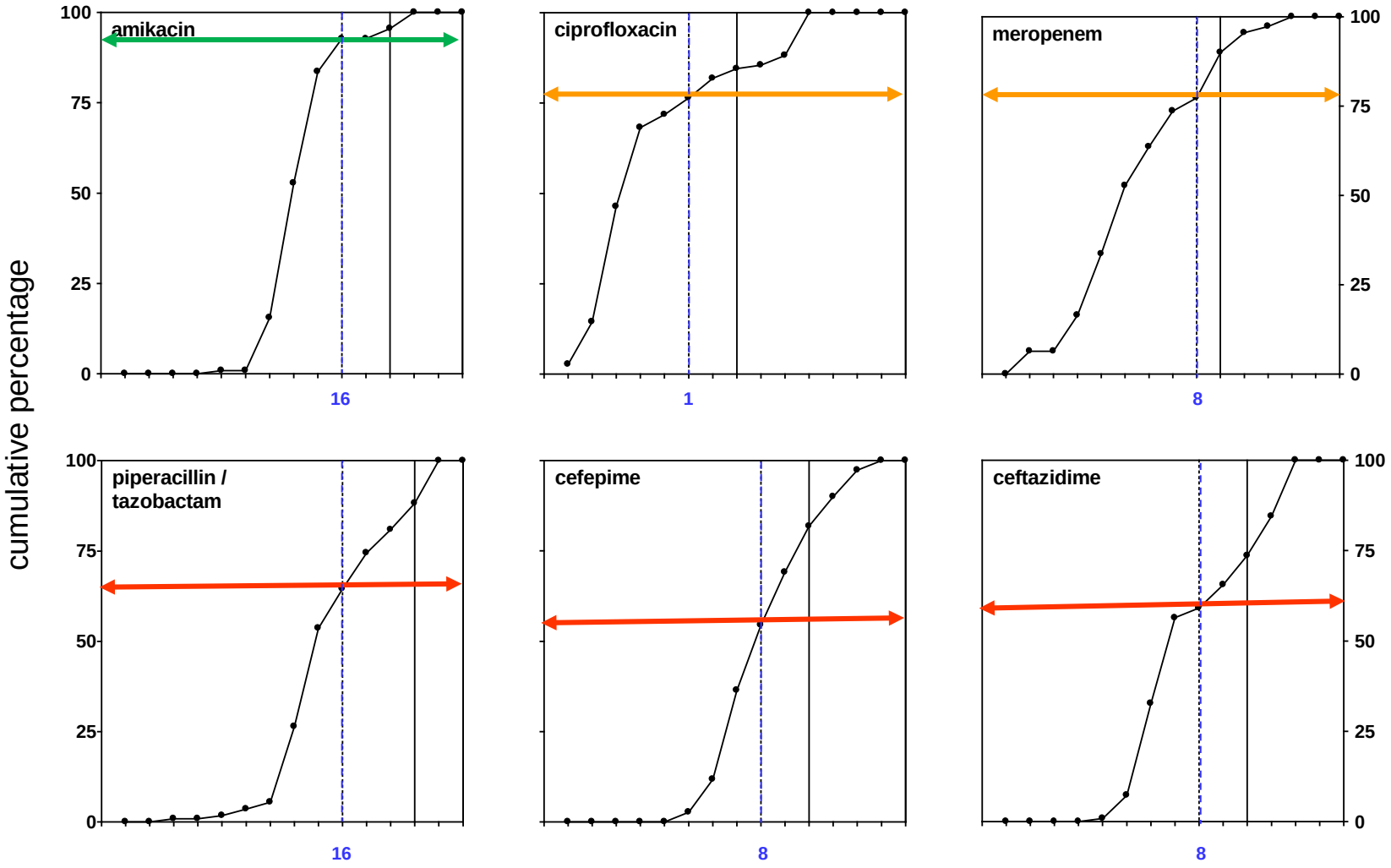
1 Henry & Speert: *Pseudomonas.* Manual of clinical microbiology. 10th ed 2011 ASM Press Washington, DC
2 Wisplinghoff. *Pseudomonas aeruginosa* and Other *Pseudomonas* spp. Infectious Diseases 4th Edition, 2017. Available on line at https://expertconsult.inkling.com/read/
3. Mathee et al. Proc Natl Acad Sci USA. 2008:105:3100-3105 – PMID 18287045

P. aeruginosa in Europe between 1997 and 2005



Mesaros *et al.* Clin Microbiol Infect. 2007;13:560-778 - PMID 17266725

P. aeruginosa in Brussels in 2007-2009

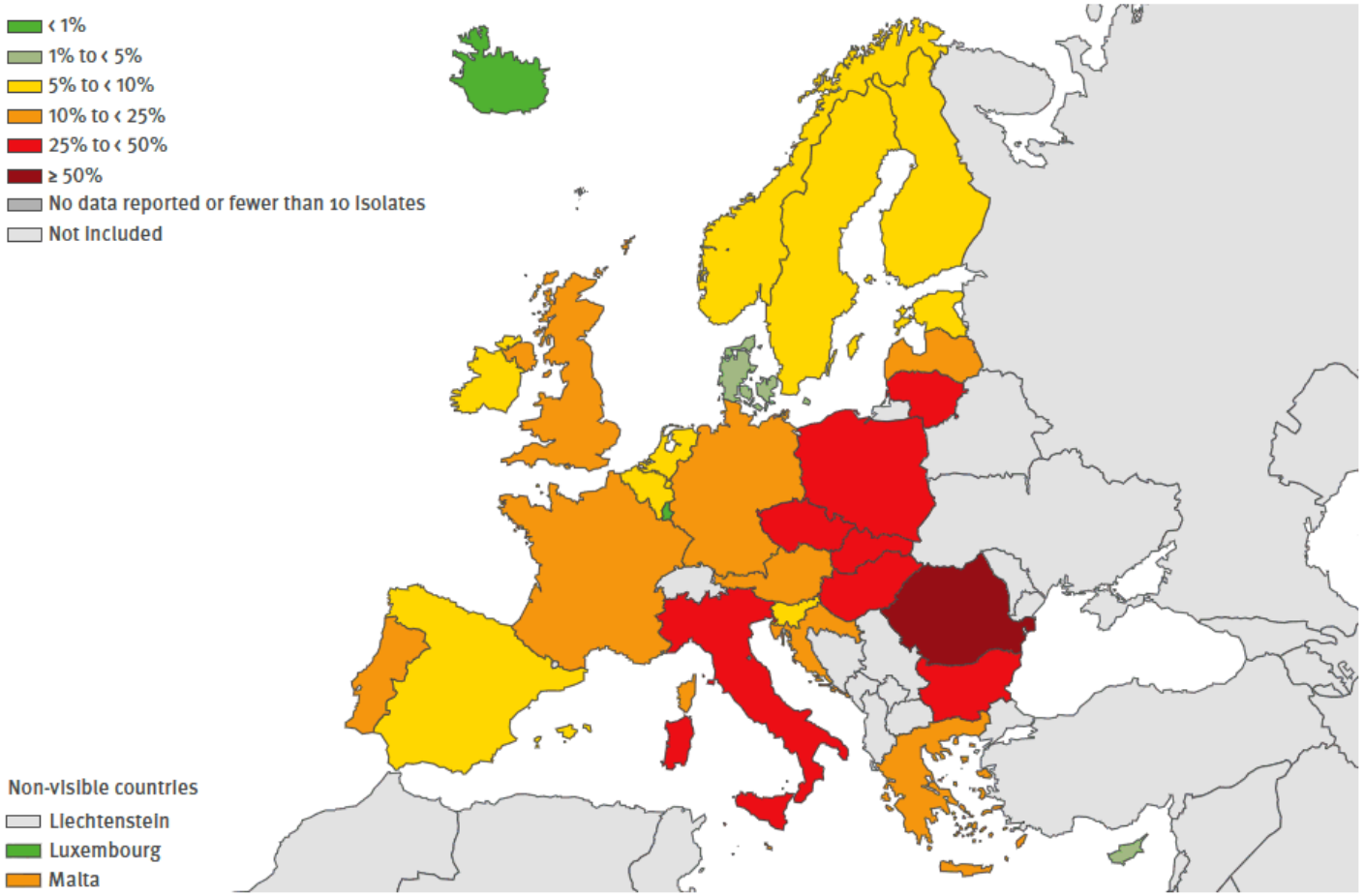


Riou *et al.* Int J Antimicrob Agents IJAA 2010;36:513-522 – PMID 20926262

The problem of multiresistance for *P. aeruginosa*

1. Piperacillin-tazobactam

Figure 3.11. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to piperacillin-tazobactam, by country, EU/EEA countries, 2015

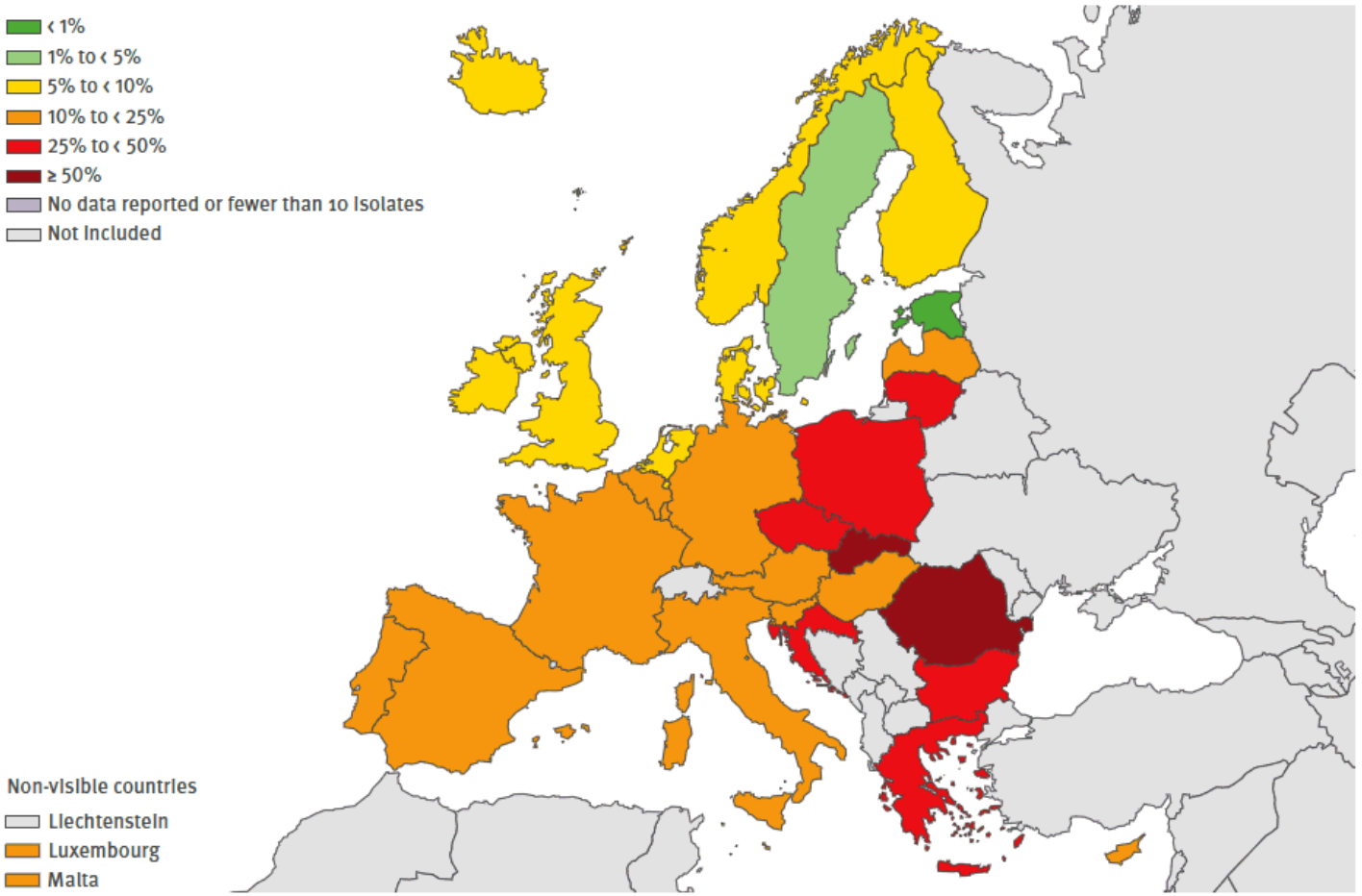


European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017.
Available from http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf (Last accessed: 20 Oct 2017)

The problem of multiresistance for *P. aeruginosa*

2. Fluoroquinolones

Figure 3.12. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2015

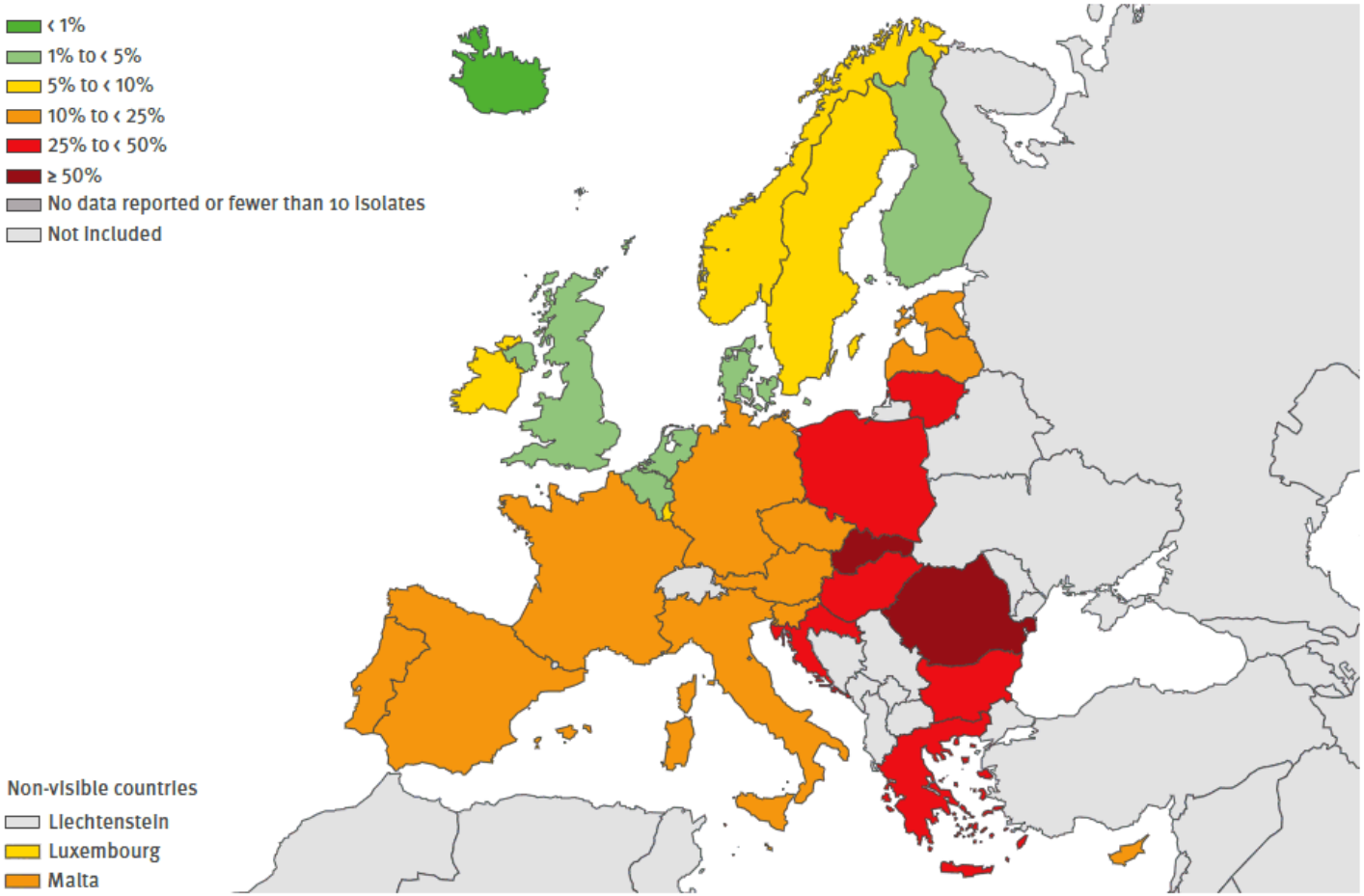


European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017.
Available from http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf (Last accessed: 20 Oct 2017)

The problem of multiresistance for *P. aeruginosa*

3. carbapenems

Figure 3.15. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2015



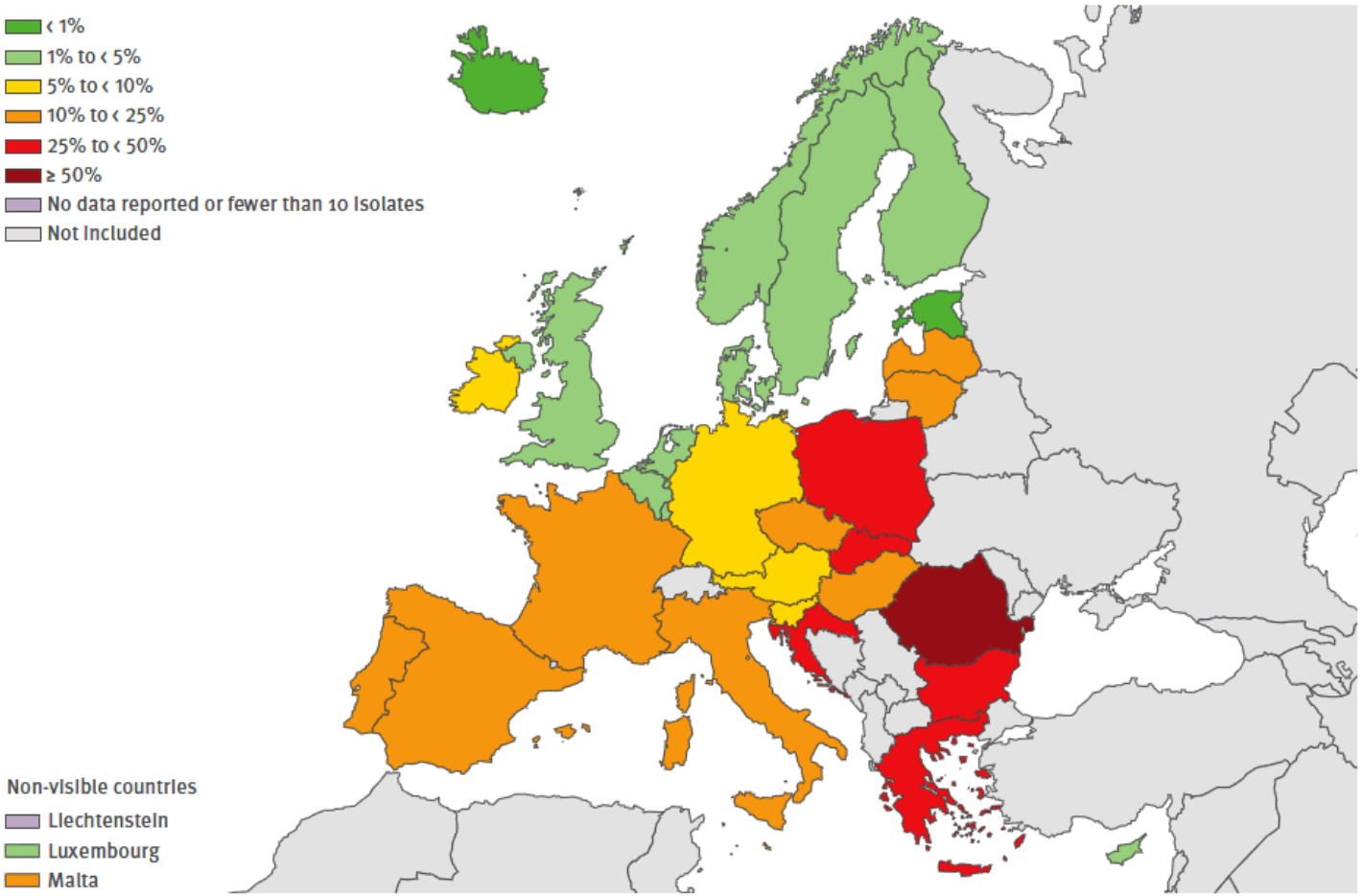
European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017.
Available from http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf (Last accessed: 20 Oct 2017)

The problem of multiresistance for *P. aeruginosa*

4. multiresistance

3 or more of these

Figure 3.16. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with combined resistance (resistance to three or more antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems), by country, EU/EEA countries, 2015



European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017.
Available from http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf (Last accessed: 20 Oct 2017)

What are the outcomes of MDR in severe infections?

American Journal of Infection Control xxx (2014) 1-4

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Brief report

The impact of multidrug resistance on outcomes in ventilator-associated pneumonia

Rudy Tedja MD [a], Amy Nowacki PhD [b], Thomas Fraser MD [a,c], Cynthia Fatica RN [c], Lori Griffiths RN [c], Steven Gordon MD [a], Carlos Isada MD [a], David van Duin MD, PhD [d,*]

[a] *Department of Infectious Diseases, Medicine Institute, Cleveland Clinic, Cleveland, OH*
[b] *Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH*
[c] *Department of Infection Prevention, Quality and Patient Safety Institute, Cleveland Clinic Foundation, Cleveland Clinic, Cleveland, OH*
[d] *Division of Infectious Diseases, University of North Carolina, Chapel Hill, NC*

Tedja, *et al. Am J Infect Control*. 2014;pii: S0196-6553(13)01428-4.

Outcomes of MDR in VAP?

American Journal of Infection Control xxx (2014) 1-4

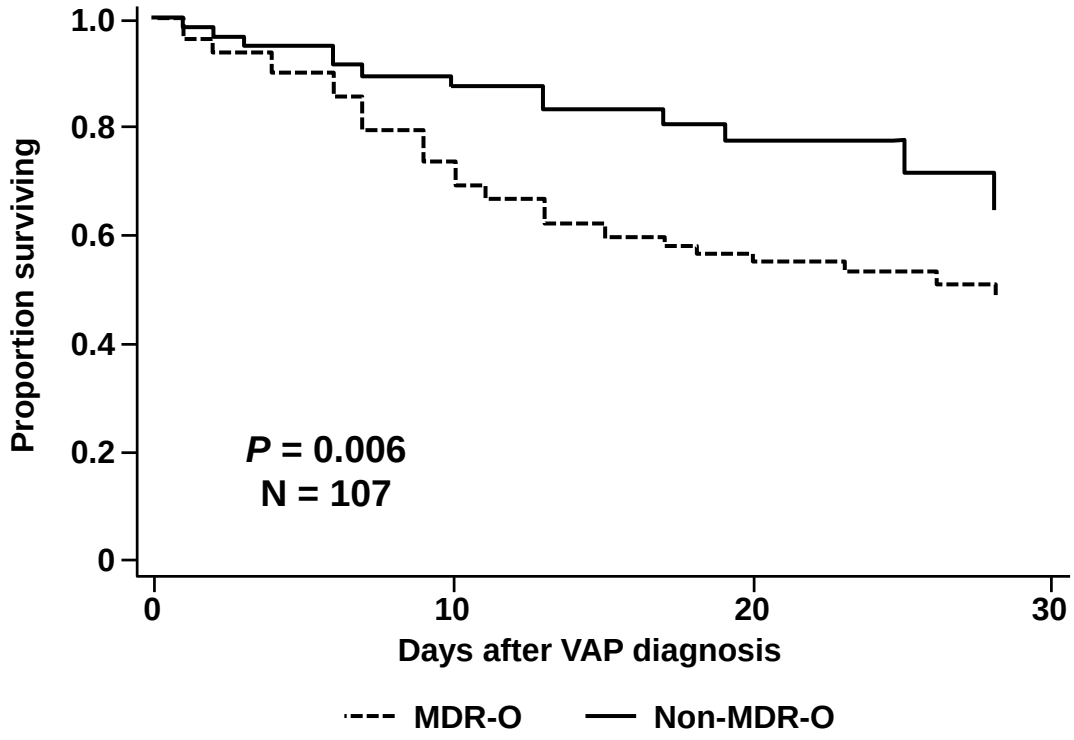
ELSEVIER

Brief report

The impact of multidrug resis
ventilator-associated pneumo

Rudy Tedja MD [a], Amy Nowacki PhD [b]
Lori Griffiths RN [c], Steven Gordon MD

[a] Department of Infectious Diseases, Medicine Institute, Clevelan
[b] Department of Quantitative Health Sciences, Cleveland Clinic,
[c] Department of Infection Prevention, Quality and Patient Safety
[d] Division of Infectious Diseases, University of North Carolina, C



Survival after diagnosis of ventilator-associated pneumonia. Time to death is shown, censored by hospital discharge. NDR-O, multidrug-resistant organism.

Tedja, *et al. Am J Infect Control*. 2014;pii: S0196-6553(13)01428-4.

Outcomes of MDR in VAP?

American Journal of Infection Control xxx (2014) 1-4

America

jour

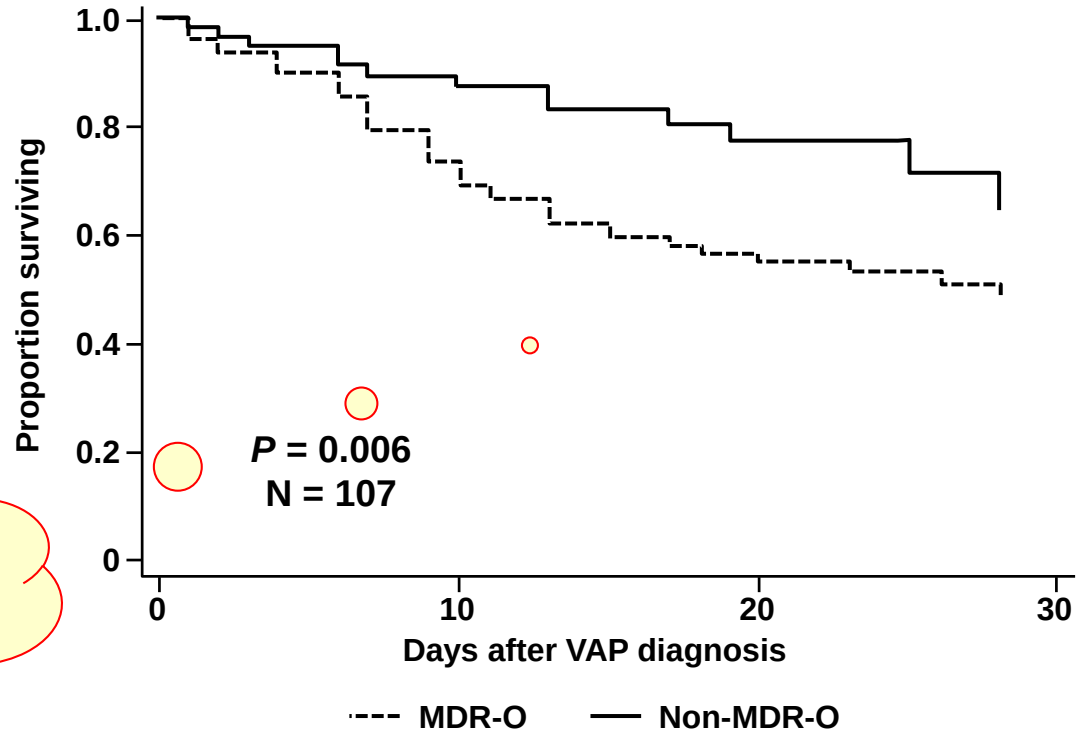
Brief report

The impact of multidrug resis
ventilator-associated pneumo

Rudy Tedja MD [a], Amy Nowacki PhD [b]
Lori Griffiths RN [c], Steven Gordon MD

[a] Department of Infectious Diseases, Medicine Institute, Clevelan
[b] Department of Quantitative Health Sciences, Cleveland Clinic, C
[c] Department of Infection Prevention, Quality and Patient Safety
[d] Division of Infectious Diseases, University of North Carolina, Ch

I guess such a difference would command a very high price for a novel antibiotic…



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Tedja, *et al. Am J Infect Control*. 2014;pii: S0196-6553(13)01428-4.

What happens if you are inadequate...

Intensive Care Med (2013) 39:682–692
DOI 10.1007/s00134-013-2828-9

ORIGINAL

Mario Tumbarello
Gennaro De Pascale
Enrico Maria Trecarichi
Teresa Spanu
Federica Antonicelli
Riccardo Maviglia
Mariano Alberto Pennisi
Giuseppe Bello
Massimo Antonelli

Clinical outcomes of *Pseudomonas aeruginosa* pneumonia in intensive care unit patients

Tumbarello, *et al Intensive Care Med*. 2013;39:682-92

What happens if you are inadequate...

Intensive Care Med (2013) 39:682–692
DOI 10.1007/s00134-013-2828-9

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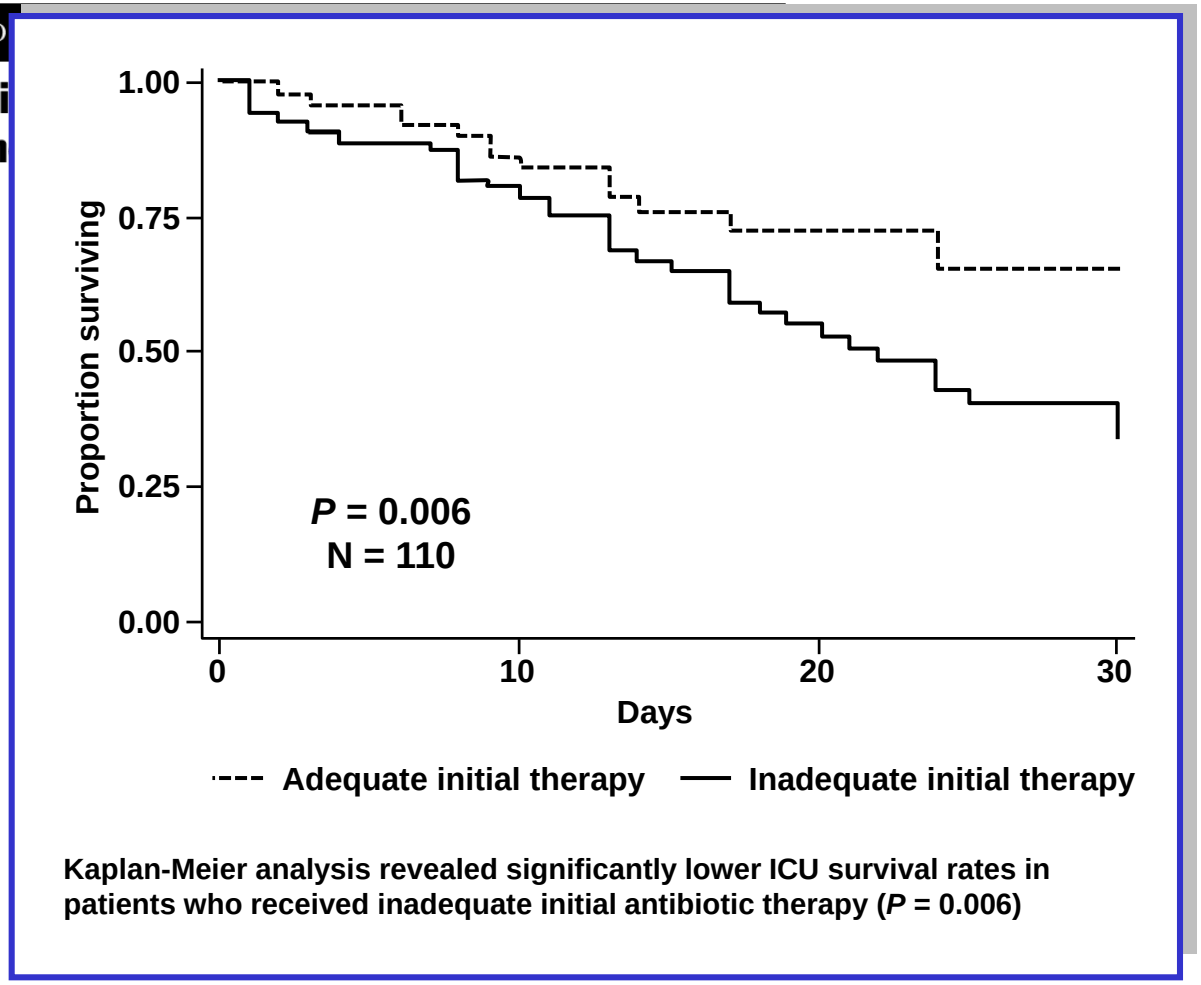

Kaplan-Meier analysis revealed significantly lower ICU survival rates in patients who received inadequate initial antibiotic therapy (*P* = 0.006)

Tumbarello, *et al. Intensive Care Med*. 2013;39:682-92

What for neutropenic patients ?

J Antimicrob Chemother 2017; **72**: 668–677
doi:10.1093/jac/dkw459 Advance Access publication 13 December 2016

Journal of Antimicrobial Chemotherapy

Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis

Elda Righi[1,2]*, Anna Maria Peri[2,3], Patrick N. A. Harris[2], Alexander M. Wailan[2], Mariana Liborio[4], Steven W. Lane[5–7] and David L. Paterson[2]

[1]Infectious Diseases Division, Santa Maria della Misericordia University Hospital, Udine, Italy; [2]The University of Queensland, UQ Centre for Clinical Research (UQCCR), Brisbane, Australia; [3]Department of Clinical and Biomedical Sciences Luigi Sacco, III Division of Infectious Diseases, University of Milan, Milan, Italy; [4]School of Medicine, Universidade de Fortaleza (UNIFOR), Fortaleza, Brazil; [5]QIMR Berghofer Medical Research Institute, Brisbane, Australia; [6]Department of Haematology, Royal Brisbane and Women's Hospital, Brisbane, Australia; [7]School of Medicine, University of Queensland, Australia

Righi e al. J Antimicrob Chemother. 2017;72:668-677 - PMID 27999023

Carbapenem resistance of Gram-negative bacteria in neutropenic patients across the world

J Antimicrob Chemother 2017; **72**: 668–677
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Journal of Antimicrobial Chemotherapy

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Elda Rig

[1]*Infectious Diseases*
for Clinical Rese
Infectious Diseases
Berghofer Medic

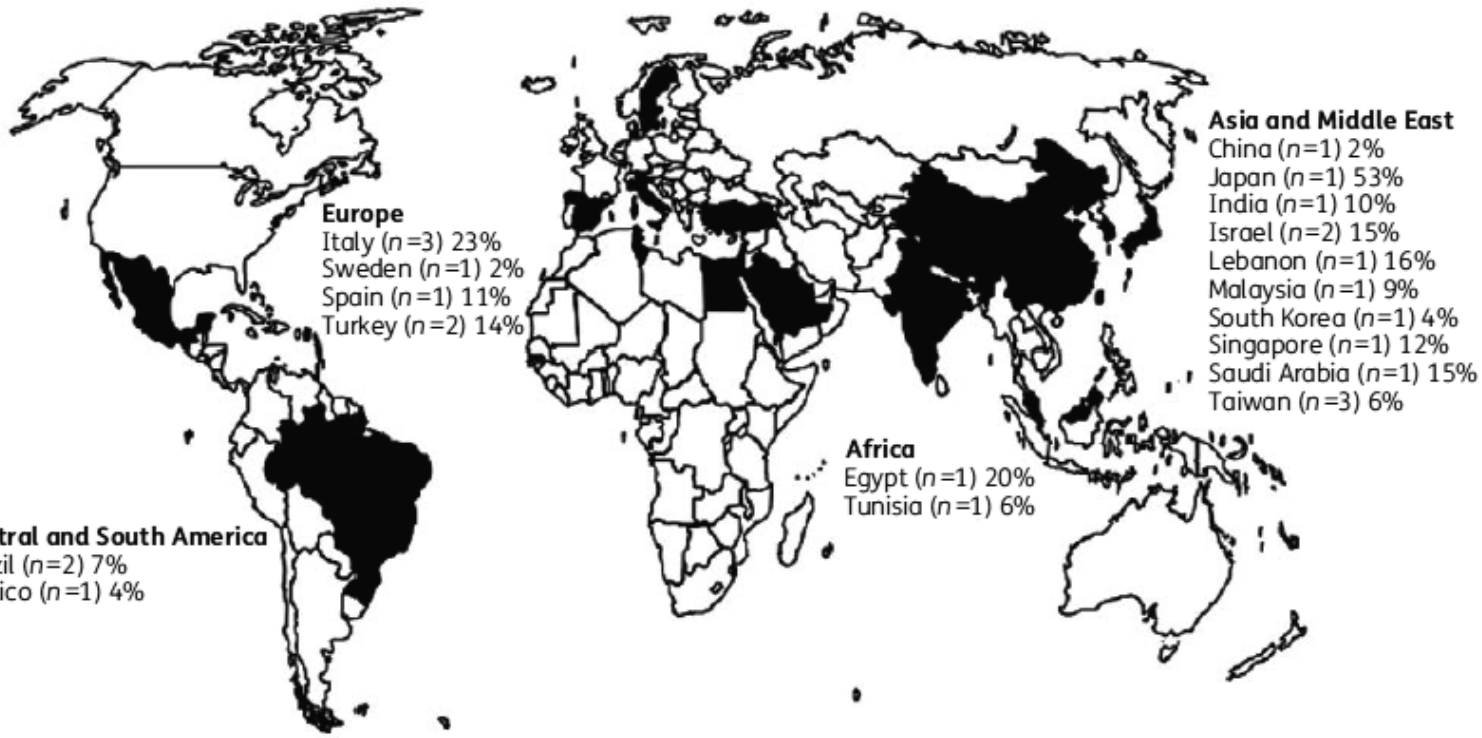

Figure 2. Geographical distribution of carbapenem resistance prevalence (%) in GNB isolated from BSIs in neutropenic patients, with number of included studies per country in parentheses.

Righi e al. J Antimicrob Chemother. 2017;72:668-677 - PMID 27999023

Resistance of Gram-negative bacteria and of *Pseudomonas* spp to antipseudomonal antibiotics in neutropenic patients

J Antimicrob Chemother 2017; **72**: 668–677
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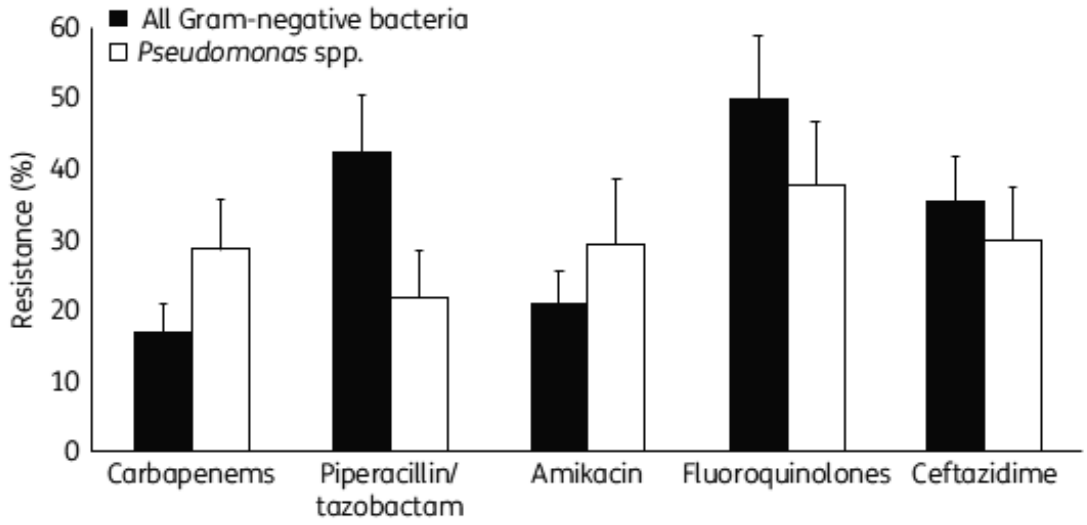
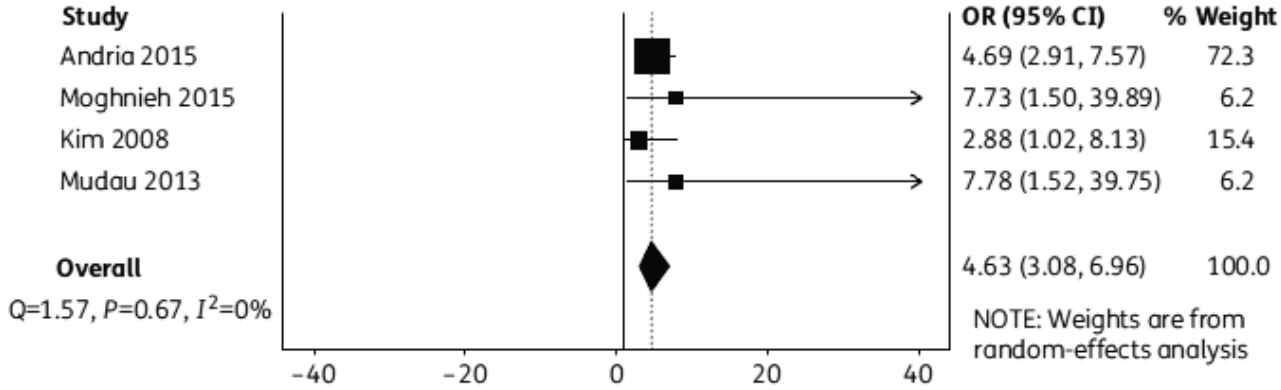


Figure 3. Percentages of resistance to carbapenems, piperacillin/tazobactam, amikacin, fluoroquinolones and ceftazidime among GNB and *Pseudomonas* spp. (expressed as percentage of all *Pseudomonas* isolates) from BSIs in neutropenic patients.

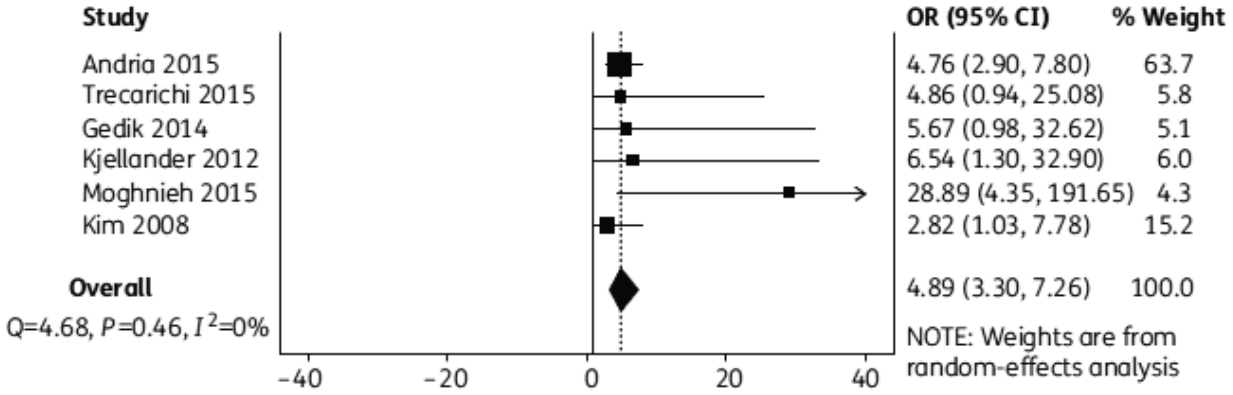
Righi e al. J Antimicrob Chemother. 2017;72:668-677 - PMID 27999023

What are the risks of carbapenem resistance for neutropenic patients ?



risk of resistance due to previous exposure to carbapenems

Figure 4. Forest plot of the association of carbapenem resistance with previous carbapenem exposure. Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight, i.e. the inverse of the variance), horizontal lines represent 95% CI and diamonds represent summary estimates with corresponding 95% CI.



risk of mortality in association with carbapenem resistance

Figure 5. Forest plot of the association of carbapenem resistance with mortality for BSIs in neutropenic patients. Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight), horizontal lines represent 95% CI and diamonds represent summary estimates with corresponding 95% CI.

Righi e al. J Antimicrob Chemother. 2017;72:668-677 - PMID 27999023

Emergence of resistance during treatment

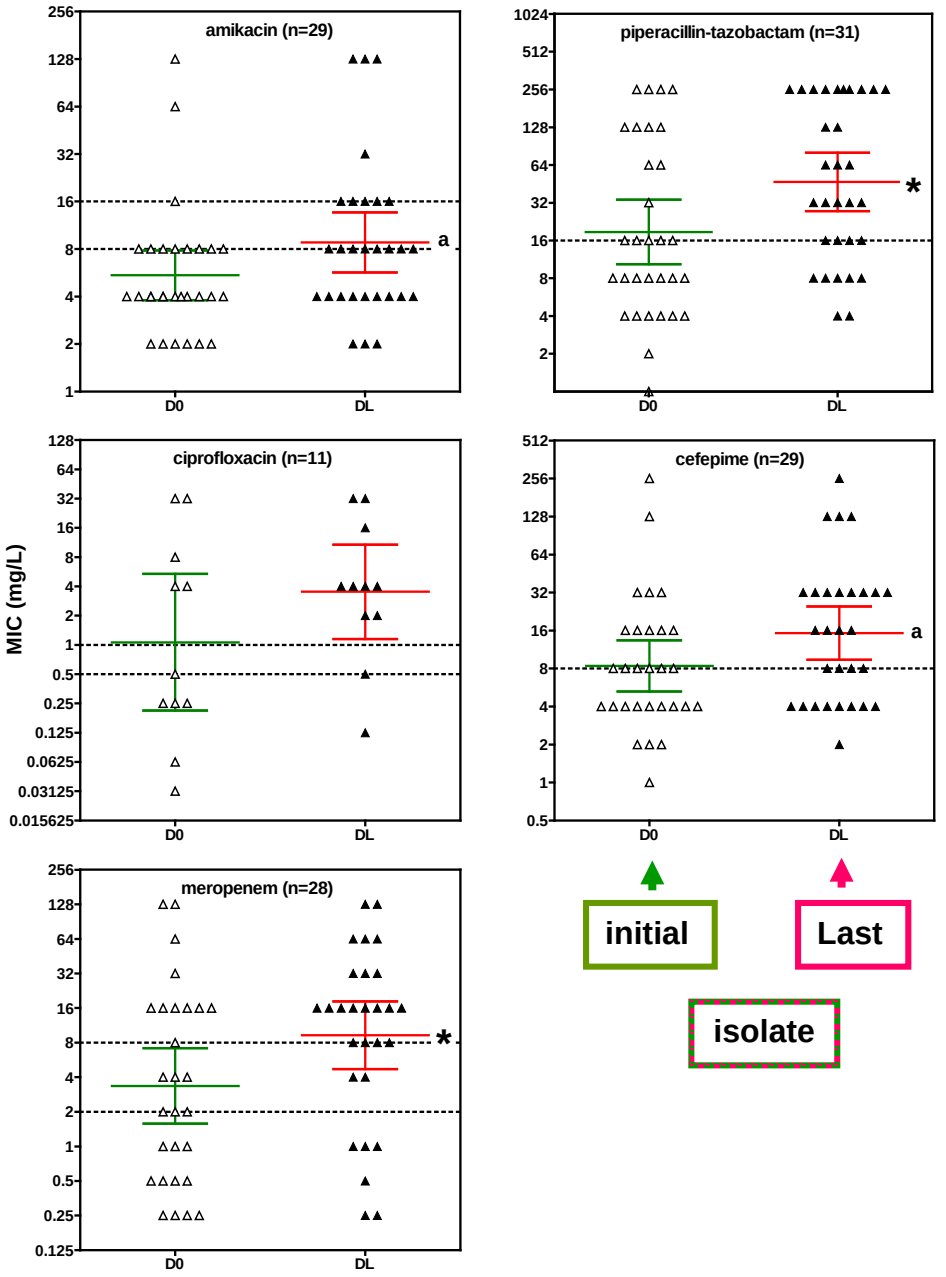
P. aeruginosa successive clonal isolates from the same patient (all patients treated with large doses of 1 to 3 antibiotics)

- D0: initial isolate
  DL: last isolate obtained
- individual values with geometric mean (95 % CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* $p < 0.05$ by paired t-test (two-tailed) and Wilcoxon non-parametric test

[a] $p < 0.05$ by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)



Riou, *et al. Int J Antimicrob Agents.* 2010;36:513-22

Emergence of resistance during treatment if persistent

Original Article

http://dx.doi.org/10.3947/ic.2013.45.3.283
Infect Chemother 2013;45(3):283-291
pISSN 2093-2340 · eISSN 2092-6448

ic Infection & Chemotherapy

Correlations between Microbiological Outcomes and Clinical Responses in Patients with Severe Pneumonia

Sungmin Kiem[1], and Jerome J. Schentag[2]

[1]Department of Internal Medicine, Inje University College of Medicine, Busan, Korea; [2]School of Pharmacy and Pharmaceutical Sciences The University at Buffalo, Buffalo, NY, USA

- **3 clinical trials (US – 1984-1993) with PK/PD optimized dosages**
- **146 bacterial strains from 76 patients**
- **non-eradicated strains (71%) already had or developed resistance**

Kiem & Schentag. *Infect Chemother.* 2013;45:283-91

Emergence of resistance during treatment if persistent ore relapse

Original Article

http://dx.doi.org/10.3947/ic.2013.45.3.283
Infect Chemother 2013;45(3):283-291
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ic Infection & Chemotherapy

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- **3 clinical trials (US – 1984-1993) with PK/PD optimized dosages**
- **146 bacterial strains from 76 patients**
- **non-eradicated strains (71%) already had or developed resistance**

Microbiological outcomes	Susceptible	Resistant	Development of resistance	Total
Enterobacter spp.[a]				12
Eradication	4	0	1	5
Persistence	0	0	3	3
Relapse	0	0	2	2
Colonization	0	2	0	2
Pseudomonas spp.[d]				31
Eradication	7	1	0	8
Persistence	4	4	9	17
Relapse	1	0	4	5
Colonization	1	0	0	1

Kiem & Schentag. *Infect Chemother.* 2013;45:283-91

What can we do ?

- **Ceftozolane** may help for *P. aeruginosa* (with tazobactam) [1,2]
- **Newly approved β-lactamase inhibitors (avibactam, vaborbactam)** may restore susceptibility to ceftazidime to a high proportion of Gram-negatives including *P. aeruginosa* [1,3]
- **Combining** antibiotics (based on checker board [4]) or associating of glycopeptides with colistin for ≥ 5 days [5] could help
- **Extended infusion** (of cefepime) may improve mortality, and decrease mean length of stay and hospital costs [6]
- **Continuous infusion** may be a promising approach in severely-ill patients [7] ... but may not solve the problem of emergence of resistance... (see next slide)

1. General review: Wright et al. Clin Microbiol Infect. 2017;23:704-712 - PMID 28893690.
2. ceftozolane/tazobactam product information: https://www.merckconnect.com/zerbaxa/overview.html
3. avibactam/ceftzidime product information: https://www.allergan.com/assets/pdf/avycaz_pi
   vaborbactam/meropenem product information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209776lbl.pdf
4. Nakamura *et al*. J Infect Chemother. 2014;20:266-269 - PMID 24486172
5. Petrosillo *et al.* Antimicrob Agents Chemother. 2014;58:851-858 - PMID 24277037
6. Bauer.*et al.* Antimicrob Agents Chemother 2013;57:2907-2912 - PMID 23571547
7. Van Herendael *et al.* Ann Intensive Care. 2012;2:22 (23 pages) - PMID 22747633
   Dulhunty *et al.* Clin Infect Dis. 2013;56:236-244 - PMID 23074313
   Lee et al. Eur J Drug Metab Pharmacokinet. 2017; Epub ahead of print - PMID 29027128

Bolus / Continuous infusion and resistance

Felton et al Antmicrob Agents Chemother 2013;57:5811-5819

Impact of Bolus Dosing versus Continuous Infusion of Piperacillin and Tazobactam on the Development of Antimicrobial Resistance in *Pseudomonas aeruginosa*

T. W. Felton,[a] J. Goodwin,[a,b] L. O'Connor,[a] A. Sharp,[a,b] L. Gregson,[a,b] J. Livermore,[a,b] S. J. Howard,[a,b] M. N. Neely,[c] W. W. Hope[a,b]

The University of Manchester, Manchester Academic Health Science Centre, NIHR Translational Research Facility in Respiratory Medicine, University Hospital of South Manchester NHS Foundation Trust, Manchester, United Kingdom[a]; Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom[b]; Laboratory of Applied Pharmacokinetics, University of Southern California, School of Medicine, Los Angeles, California, USA[c]

Felton *et al* Antimicrob Agents Chemother 2013;57:5811-5819 – PMID 24002098

What do we need for efficacy ?

AAC Journals.ASM.org

Impact of Bol
and Tazobacta
Pseudomonas

T. W. Felton,[a] J. Goodwin,
The University of Manchester, Ma
Manchester NHS Foundation Tru
Pharmacology, University of Live
Angeles, California, USA[c]

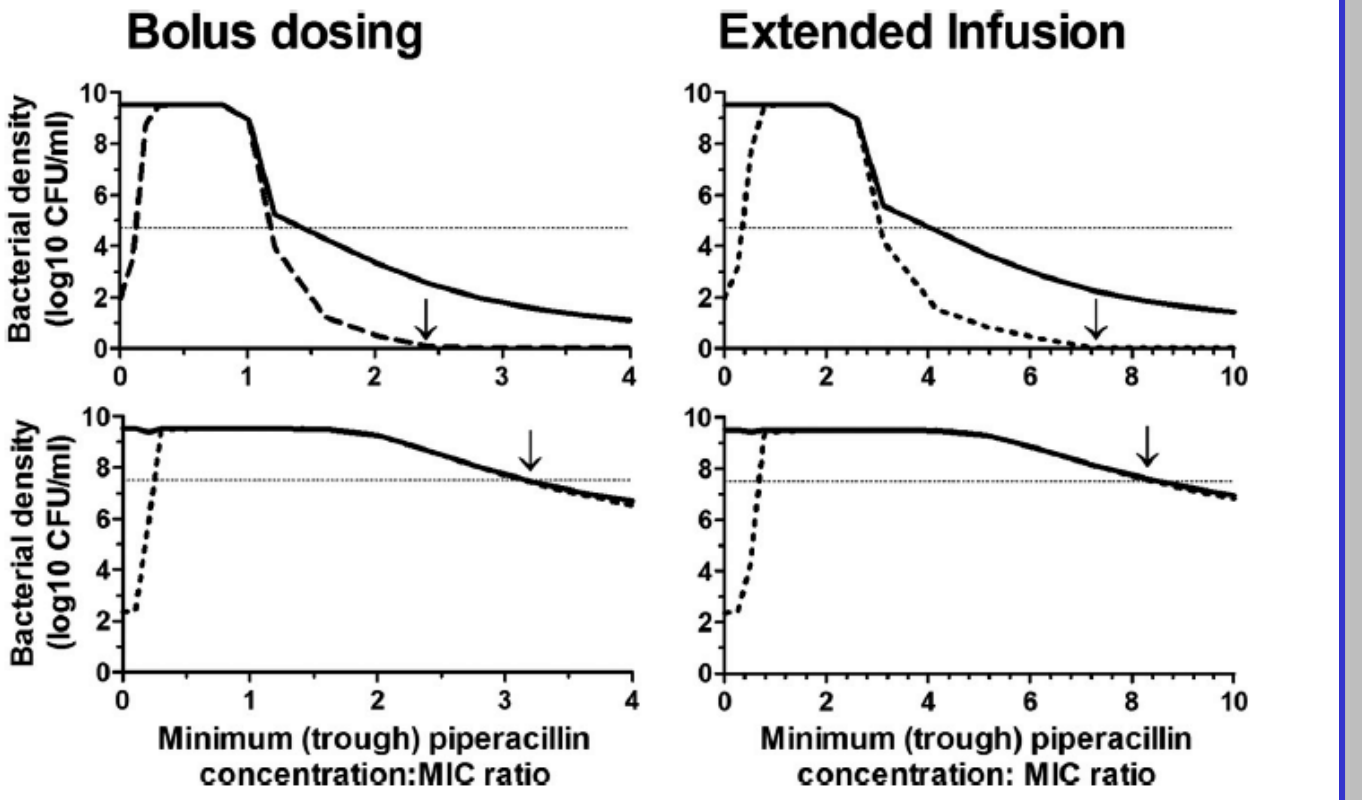


FIG 7 Change in bacterial density with the trough free piperacillin/MIC ratio following 5 days of treatment and target attainment of clinical regimens. Solid line, total population; dashed line, resistant subpopulation; dotted line, stasis line. The arrow indicates the relevant C_{min}/MIC ratio.

Felton *et al* Antimicrob Agents Chemother 2013;57:5811-5819 – PMID 24002098

What do we need for suppression of resistance?

Impact of Bolus Dosing
and Tazobactam on the
Pseudomonas aeruginosa

T. W. Felton,[a] J. Goodwin,[a,b] L. O'Connor,[a] A.
The University of Manchester, Manchester Academic Hea
Manchester NHS Foundation Trust, Manchester, United K
Pharmacology, University of Liverpool, Liverpool, United
Angeles, California, USA[c]

Will you ever be able to achieve such high C_{min} blood levels ?

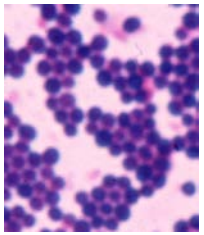
TABLE 3 C_{min}/MIC ratios required to achieve stasis, 1-, 2-, and 3-log bacterial killing and suppression of emergence of resistance

Bacterial density and status	C_{min}/MIC (mg/liter)			
	Bolus		Extended infusion	
	Hollow fiber	Predicted plasma[a]	Hollow fiber	Predicted plasma[a]
Low				
Bacterial stasis (total bacteria)	1.4	2.0	4.1	5.9
1-log reduction in total CFU/ml	1.8	2.6	5.2	7.4
2-log reduction in total CFU/ml	2.4	3.4	6.7	9.6
3-log reduction in total CFU/ml	3.2	4.6	8.8	12.6
Suppression of resistance	2.4	3.4	7.3	10.4
High				
Bacterial stasis (total bacteria)	3.2	4.6	8.3	11.9

[a] Protein binding is assumed to be 30% (31).

Felton *et al* Antimicrob Agents Chemother 2013;57:5811-5819 – PMID 24002098

Staphylococcus aureus



http://www.microbeworld.org/index.php?option=com_jlibrary&view=article&id=7611

The *S. aureus* saga: from the origins to penicillin

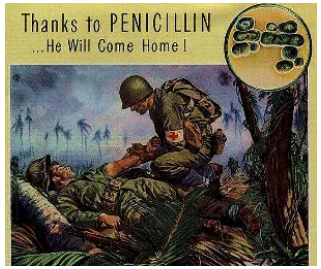
1881:
First observation of staphylococci in pus by Alexander Ogston

"Micrococci so deleterious when injected are seemingly harmless on the surface of wounds and ulcers".
Br Med J
1881;1:369e375

1884:
First distinction between *S. aureus* and *S. albus* by Friedrich Rosenbach

1914-1918:
Half of the casualties in the trenches of the First World War were due to septic wound infections with *S. aureus*.

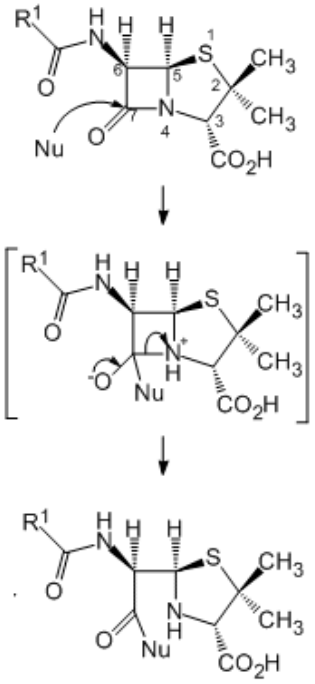
1940-45:
the production process for penicillin (then still universally active against the bacterium*) was a military secret



*** the original observation of Fleming (1928) was made on *S. aureus***

The *S. aureus* saga: from penicillin to methicillin

1944:
First description of a β-lactamase in *S. aureus* *



Lee, S. (2008). State of C2/C3 substituents of ?-lactam antibiotics in the β-lactam ring cleavage by β-lactamases. *PHILICA.COM Article number 122.*

*** The first description of a β-lactamase was made in 1940 in *E. coli* (Nature 146, 837 (28 December 1940)**

1950-70:
almost all strains of *S. aureus produce a* β-lactamase

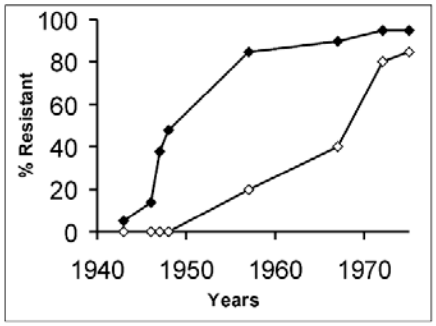


Figure. Secular trends of approximate prevalence rates for penicillinase-producing, methicillin-susceptible strains of *Staphylococcus aureus* in hospitals (closed symbols) and the community (open symbols).

1960:
introduction of methicillin … and emergence of resistance to methicillin in 1961

MICROBIOLOGICAL STUDIES ON SODIUM 6-(2,6 DIMETHOXYBENZAMIDO) PENICILLANATE MONOHYDRATE (BRL 1241) IN VITRO AND IN PATIENTS

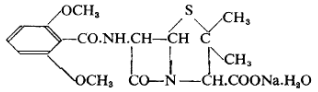
BY

G. T. STEWART, M.D., B.Sc.

With the Technical Assistance of
PATRICIA M. HARRISON, B.Sc., and
R. J. HOLT, F.I.M.L.T.

From Queen Mary's Hospital for Children and the Medical Research Council Laboratories, Carshalton, Surrey

A report in 1959 by Batchelor *et al.* on the isolation of 6-aminopenicillanic acid drew attention to the possibility of synthesizing new forms of penicillin by the introduction of side-chains. Derivatives prepared in this way may or may not possess antibacterial activity, but we were particularly impressed by the range and mode of action of one derivative, supplied to us in 1959 as BRL 1241 ("celbenin"). The compound—sodium 6-(2,6 dimethoxybenzamido)penicillanate monohydrate—may be represented by the following structural formula:



Methicillin-resistant staphylococci

MARY BARBER

From the Department of Bacteriology, Postgraduate Medical School of London

SYNOPSIS Eighteen strains of *Staph. pyogenes* (nine penicillin-sensitive and nine penicillin-destroying) were passaged 40 to 50 times on Celbenin[1] ditch plates.

All strains developed an increase in resistance to Celbenin and eight strains (four penicillin-sensitive and four penicillin-destroying) were able to grow in 100 μg/ml. or more Celbenin. Resistance was of the drug-tolerant type and none of the cultures inactivated Celbenin. There was an associated increase in tolerance to benzyl penicillin.

The highly Celbenin-resistant cultures isolated from penicillin-destroying staphylococci were in sharp contrast to those from penicillin-sensitive strains, as well as to penicillin G-tolerant staphylococci isolated *in vitro*, because they retained the cultural characteristics, coagulase and haemolytic activity, and mouse virulence of the parent strains, and the degree of resistance remained stable after repeated passage in the absence of Celbenin.

Three naturally occurring Celbenin-resistant strains of *Staph. pyogenes* isolated from infective processes were also studied. All three strains grew luxuriantly in concentrations of Celbenin up to 12·5 μg/ml. but very poorly in higher concentrations.

The possible significance of these findings is discussed.

The *S. aureus* saga: from methicillin to vancomycin

1970's:
Spreading of methicillin resistance In hospitals

1980's:
Large scale re-introduction of vancomycin *

1997:
Strains with reduced susceptibility to vancomycin

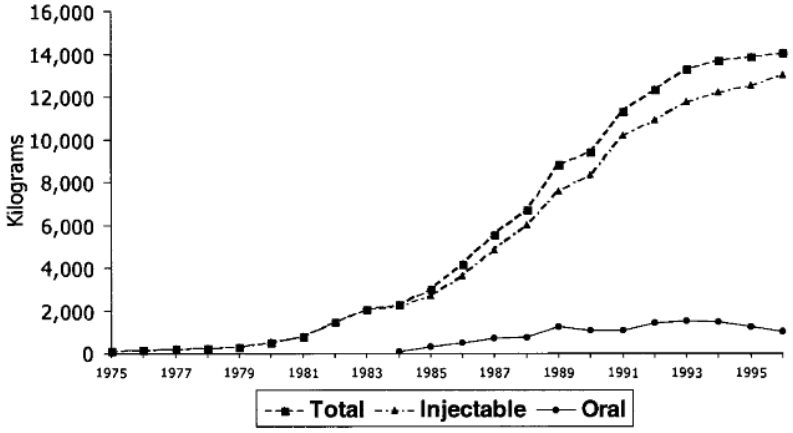


FIG. 1. Usage of vancomycin (in kilograms) in the United States, France, Italy, Germany, United Kingdom, and The Netherlands.

Kirst et al. Antimicrob Agents Chemother. 1998: 42:1303-4.

Journal of Antimicrobial Chemotherapy (1997) **40**, 135–146

Correspondence

Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility

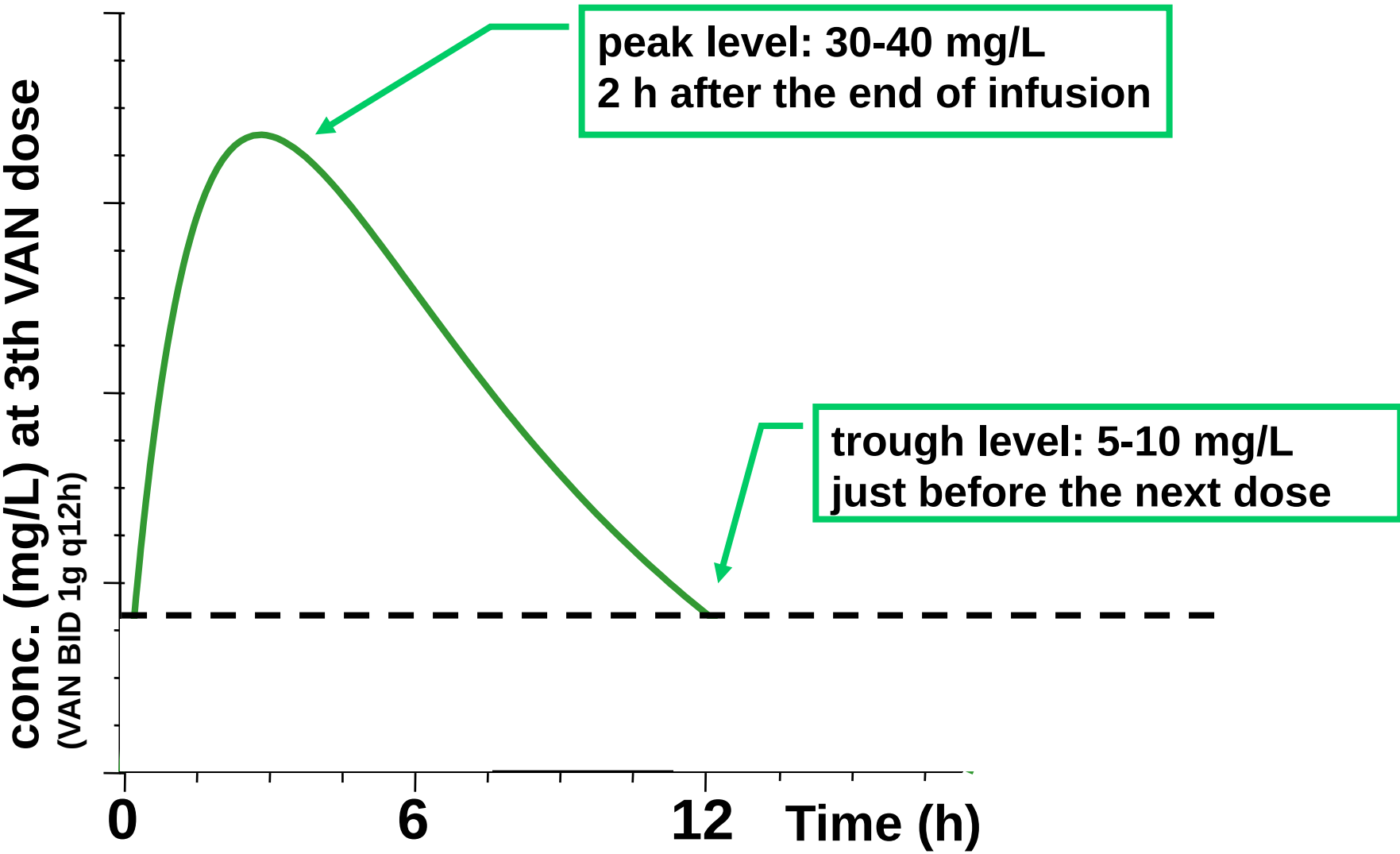
J Antimicrob Chemother 1997; **40:** 135–136

K. Hiramatsu[a*], H. Hanaki[a], T. Ino[b], K. Yabuta[b], T. Oguri[c] and F. C. Tenover[d]

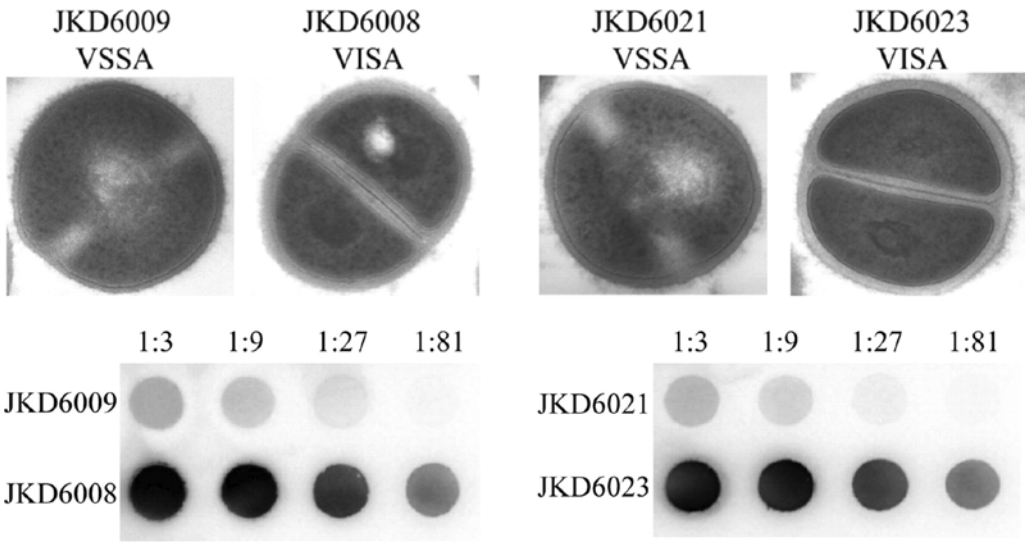
[a]*Department of Bacteriology;* [b]*Department of Pediatrics, Juntendo University, Tokyo;* [c]*Clinical Laboratory, Juntendo Hospital, Tokyo, Japan;* [d]*Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA*

*** Vancomycin was described in 1955-57**
(Antibiot Annu. 1955-1956;3:606-322 and 1956-57;4:75-122)

Vancomycin (in the good old time)



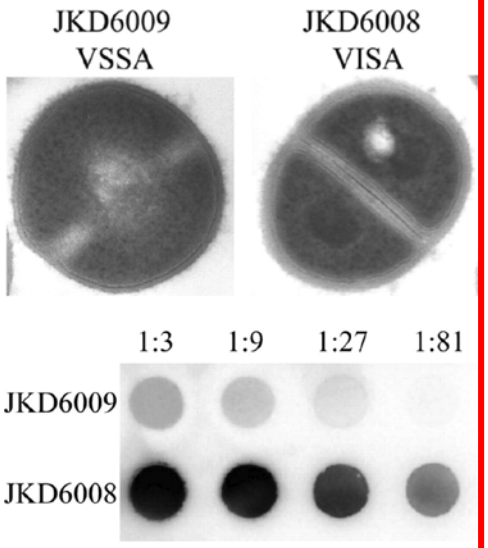
Vancomycin: emergence of the VISA strains…



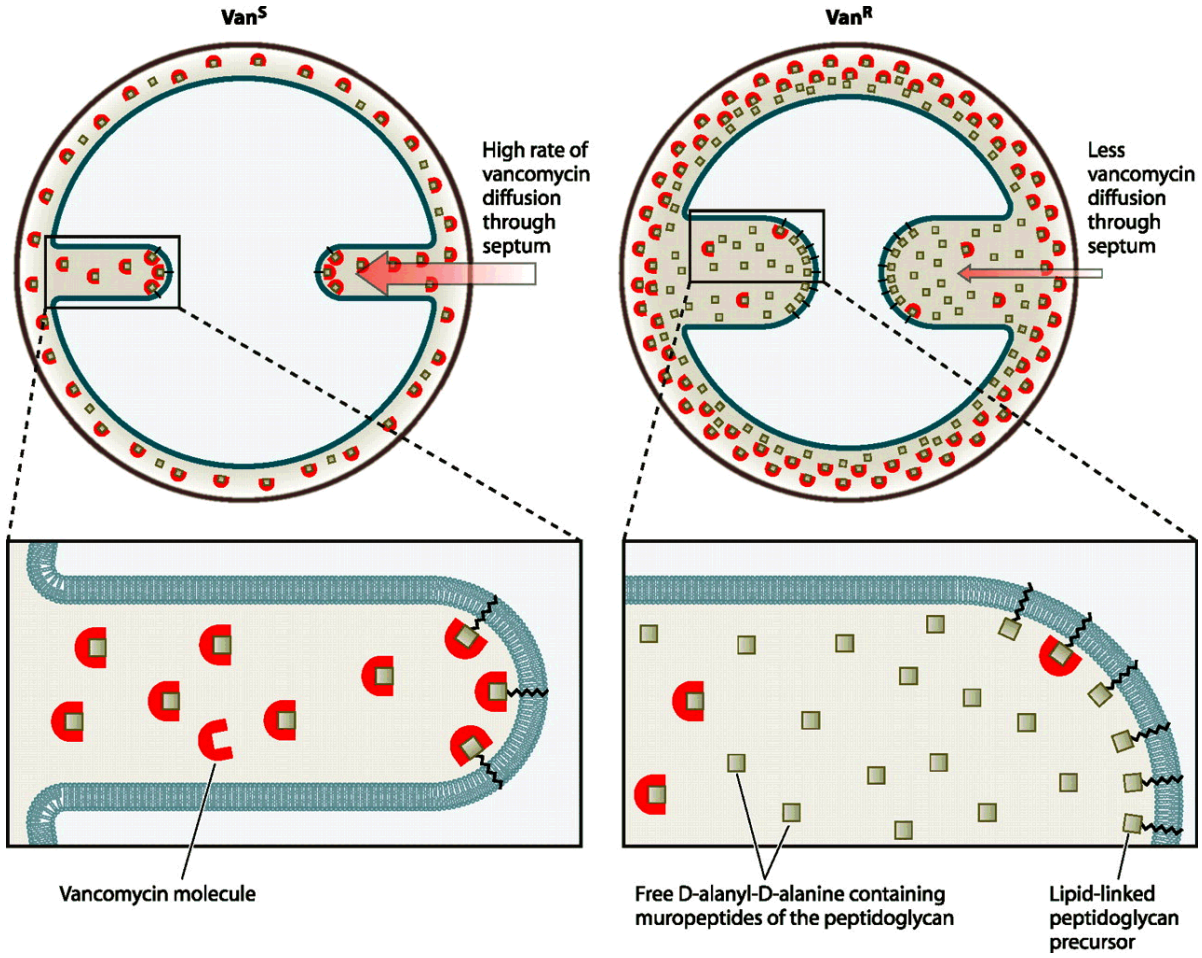
Example of the cell wall and capsule changes that occur in hVISA and VISA strains in paired isolates from patients with persistent infections.
Top: significant cell wall thickening in VISA strains compared to VSSA strains;
Bottom : increases in the expression of capsule by using an anticapsule type 8 immunoblot

Howden et al. Clin Microbiol Rev. 2010;23:99-139 - PMID 20065327

Vancomycin: emergence of the VISA strains…



Example of the cell wall and capsule changes
from patients with persistent infections.
Top: significant cell wall thickening in VISA str
Bottom : increases in the expression of capsul



Changes associated with the VISA phenotype. In vancomycin-intermediate cells (Vanr), the rate of diffusion of vancomycin molecules to the septal tip is decreased, lowering the effective concentration of antibiotic that reaches the lipid-linked peptidoglycan precursor (lipid II) at the site of cell wall synthesis

Howden et al. Clin Microbiol Rev. 2010;23:99-139 - PMID 20065327

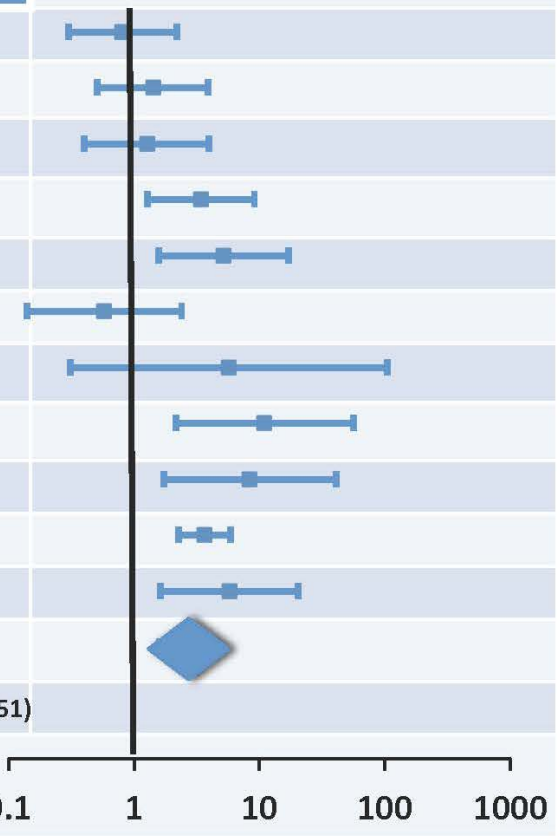
Vancomycin: the risk of elevated MICs

Forest plot using Mantel–Haenszel analysis

Study or subgroup	High MIC ≥1.5 µg/mL Events	High MIC ≥1.5 µg/mL Total	Low MIC <1.5 µg/mL Events	Low MIC <1.5 µg/mL Total	Weight	Odds ratio M-H, Random, 95% CI
Bae et al.	14	37	12	28	10.9%	
Choi et al.	12	34	10	36	10.8%	
Ferry et al.	9	24	9	28	9.7%	
Hidayat et al.	20	51	7	44	11.0%	
Hsu et al.	17	45	4	38	9.3%	
Lalueza et al.	3	13	17	50	7.7%	
Lodise et al.	6	66	0	26	2.7%	
Moise et al.	11	14	5	20	6.0%	
Moise-Broder et al.	23	25	22	38	6.8%	
Takesue et al.	34	97	85	662	15.9%	
Yoon et al.	14	18	17	45	8.8%	
Total (95% CI)		424		1015	100%	
Total events	163		188			

OR 2.69 (1.60, 4.51)

Heterogeneity: $Tau^2 = 0.38$; $c^2 = 22.59$, df 10 (P = 0.01); $I^2 = 56\%$. Test for overall effect: Z = 3.75 (P = 0.0002)



CI: confidence interval; df: degrees of freedom; MIC: minimum inhibitory concentration; MRSA: methicillin-resistant *Staphylococcus aureus*; OR: odds ratio

Van Hal SJ, et al. Clin Infect Dis 2012;54:755–771.

Vancomycin in 2011

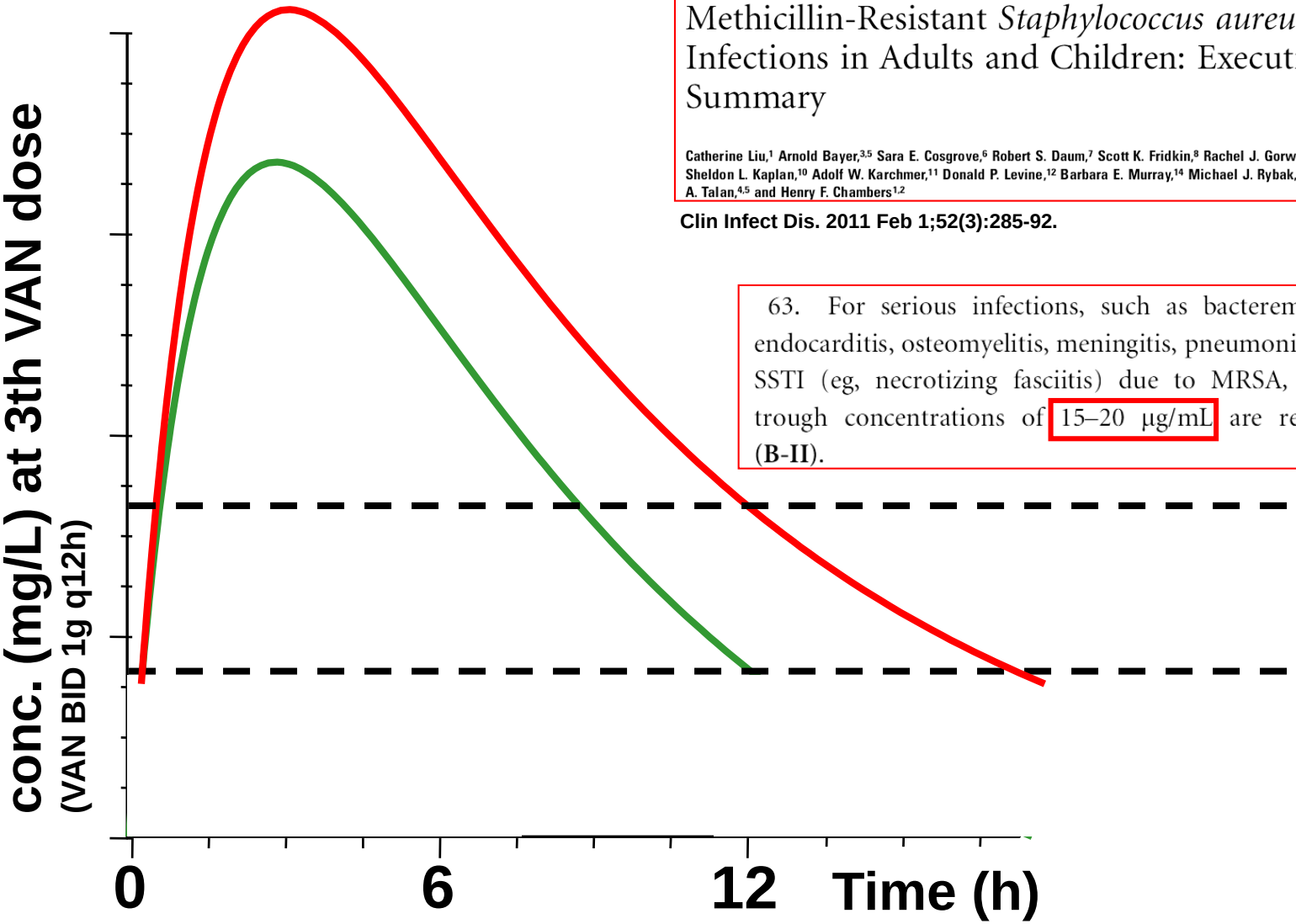
IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children: Executive Summary

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

Clin Infect Dis. 2011 Feb 1;52(3):285-92.

63. For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 μg/mL are recommended (**B-II**).



Vancomycin in 2013

Hall *et al. BMC Pharmacology and Toxicology* 2013, **14**:12
http://www.biomedcentral.com/2050-6511/14/12

BMC Pharmacology & Toxicology

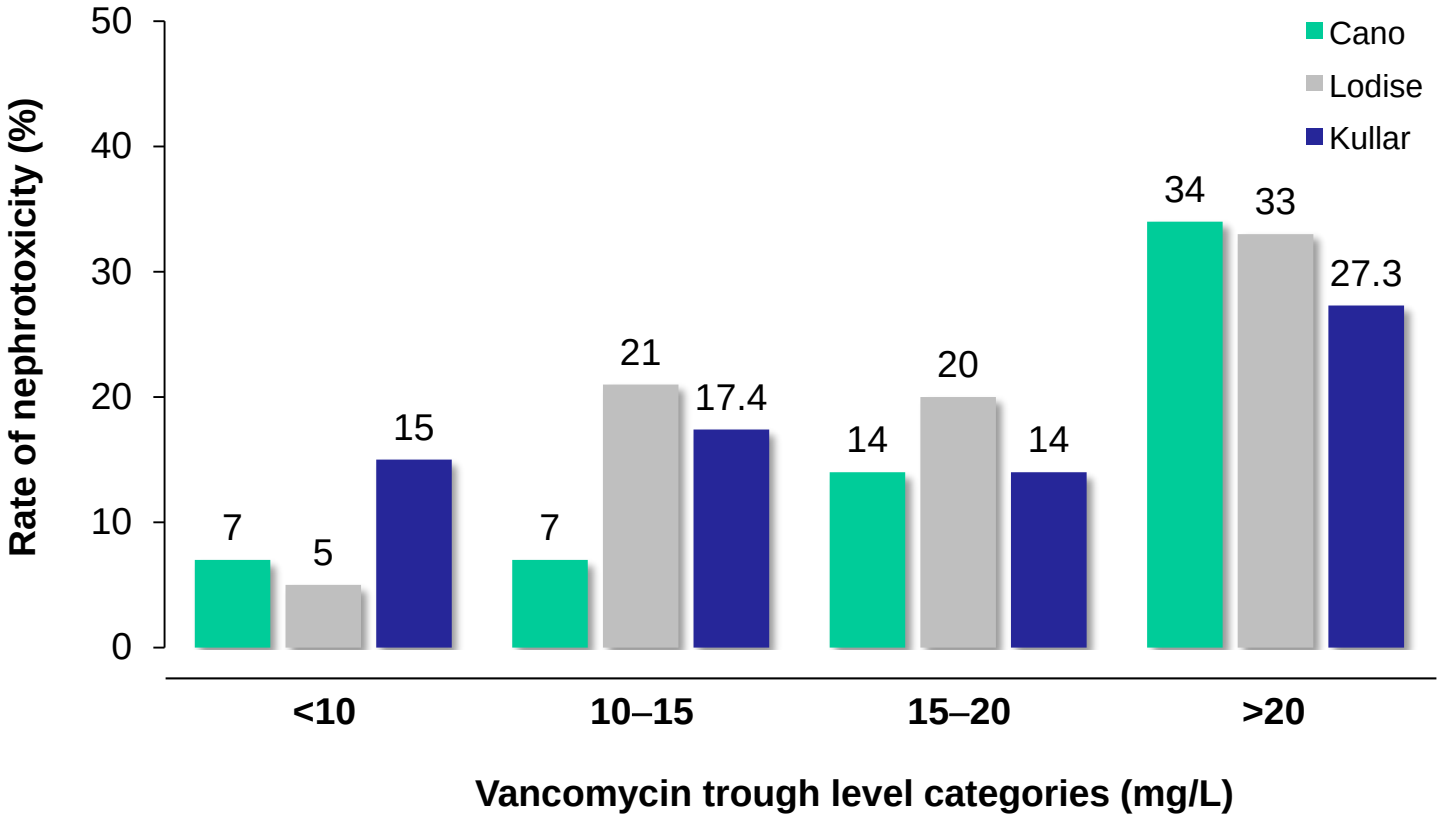
RESEARCH ARTICLE Open Access

Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study

Ronald G Hall II[1,2*], Kathleen A Hazlewood[1,7], Sara D Brouse[1,8], Christopher A Giuliano[3,9], Krystal K Haase[3], Chistopher R Frei[4], Nicolas A Forcade[4,10], Todd Bell[5], Roger J Bedimo[6] and Carlos A Alvarez[1,2]

Nephrotoxicity occurred in 78 patients (23%), occurring in 56%, 11%, and 33% of patients at Hospitals A, B, and C, respectively. The median (interquartile range) increase from baseline to peak serum creatinine was 0.0 mg/dL (0.0, 0.2) for patients who did not develop nephrotoxicity versus 1.0 mg/dL (0.6, 2.1) for patients who developed nephrotoxicity. Fifteen percent of patients had a vancomycin trough concentration greater than 20 mcg/ml. Concurrent nephrotoxins included contrast dye (34%), aminoglycosides (19%), and vasopressors (12%). Concomitant antimicrobials active against MRSA were used in 23% of patients.

Increased dosages of vancomycin lead to more toxicity

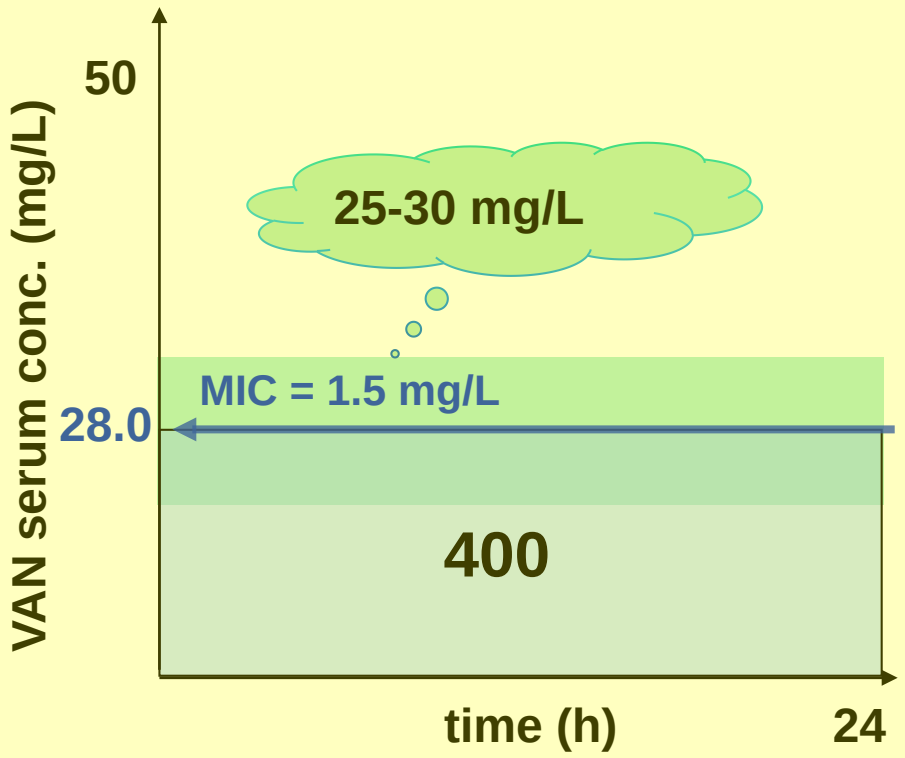


AUC: area under the concentration curve; BMD: broth microdilution; MIC: minimum inhibitory concentration; MRSA: methicillin-resistant *Staphylococcus aureus*

1. Cano EL, et al. Clin Ther 2012;34(1):149–157; 2. Kullar R, et al. Pharmacotherapy 2012;32(3):195–201; 3. Lodise TP, et al. Clin Infect Dis 2009;49:507–514

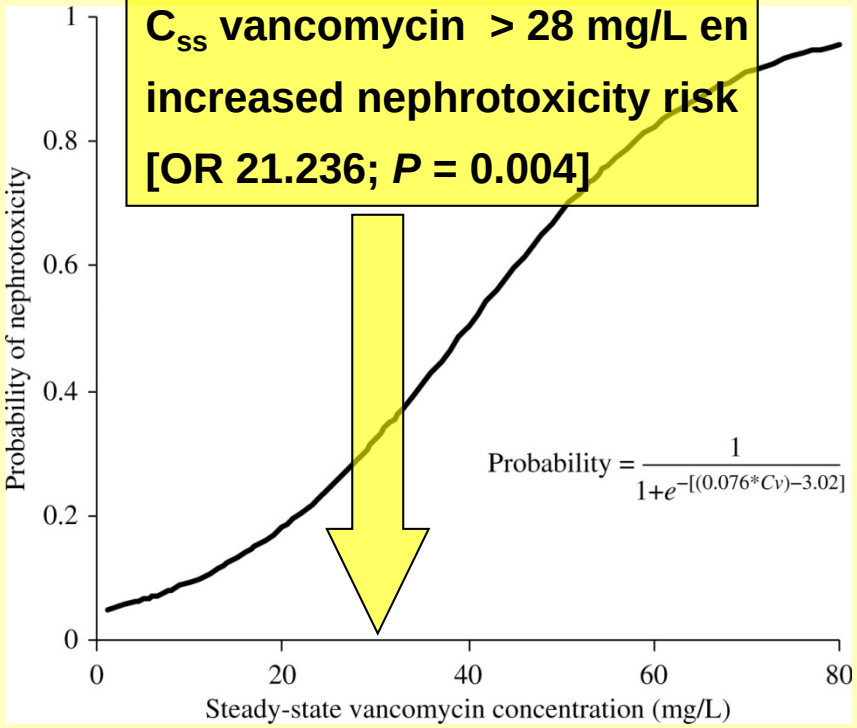
Vancomycin: will continuous infusion help ?

efficacy



Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

toxicity



Ingram, P. R. et al. J. Antimicrob. Chemother. 2008 Jul;62 (1): 168-71.

Staphylococcus aureus and linezolid

1996:
First description of linezolid

J. Med. Chem. **1996**, *39*, 673−679

Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections

Steven J. Brickner,* Douglas K. Hutchinson, Michael R. Barbachyn, Peter R. Manninen, Debra A. Ulanowicz, Stuart A. Garmon, Kevin C. Grega, Susan K. Hendges, Dana S. Toops, Charles W. Ford, and Gary E. Zurenko
Upjohn Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received December 22, 1995[®]

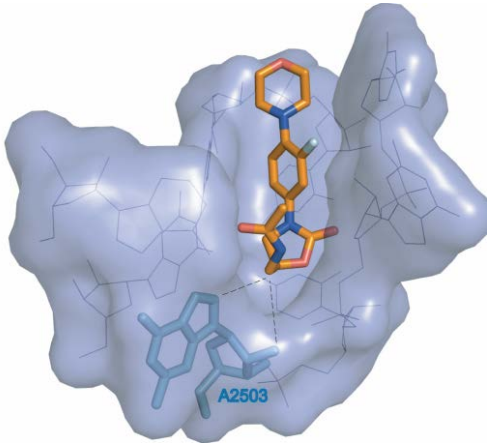
Table 1. *In Vitro* Antibacterial Activity, Minimum Inhibitory Concentration (μg/mL)

organism	strain number	U-100592	U-100766	vancomycin
Staphylococcus aureus	UC[a] 9213	4	4	1
Staphylococcus aureus[c]	UC 12673	2	4	1
Staphylococcus aureus	ATCC[b] 29213	4	4	1
Staphylococcus epidermidis	UC 30031	1	1	1
Enterococcus faecalis	ATCC 29212	2	4	4
Enterococcus faecium	UC 12712	1	2	0.5
Streptococcus pneumoniae	UC 9912	0.5	1	0.5
Streptococcus pyogenes	UC 152	1	2	0.5
Bacteroides fragilis	ATCC 25285	1	1	>16[d]
Clostridium perfringens	ATCC 13124	1	1	1[e]
Mycobacterium tuberculosis	H37Rv	≤0.125	≤0.125	*f*

[a] Upjohn Culture (registered trademark of The Upjohn Co.).
[b] American Type Culture Collection.
[c] MRSA.
[d] Comparative control value for clindamycin was 0.5 μg/mL.
[e] Comparative control value for clindamycin was 0.06 μg/mL.
[f] Comparative control value for isoniazid was 0.20 μg/mL.

1998-2002:
Resistance to linezolid by target mutation (remains rate)

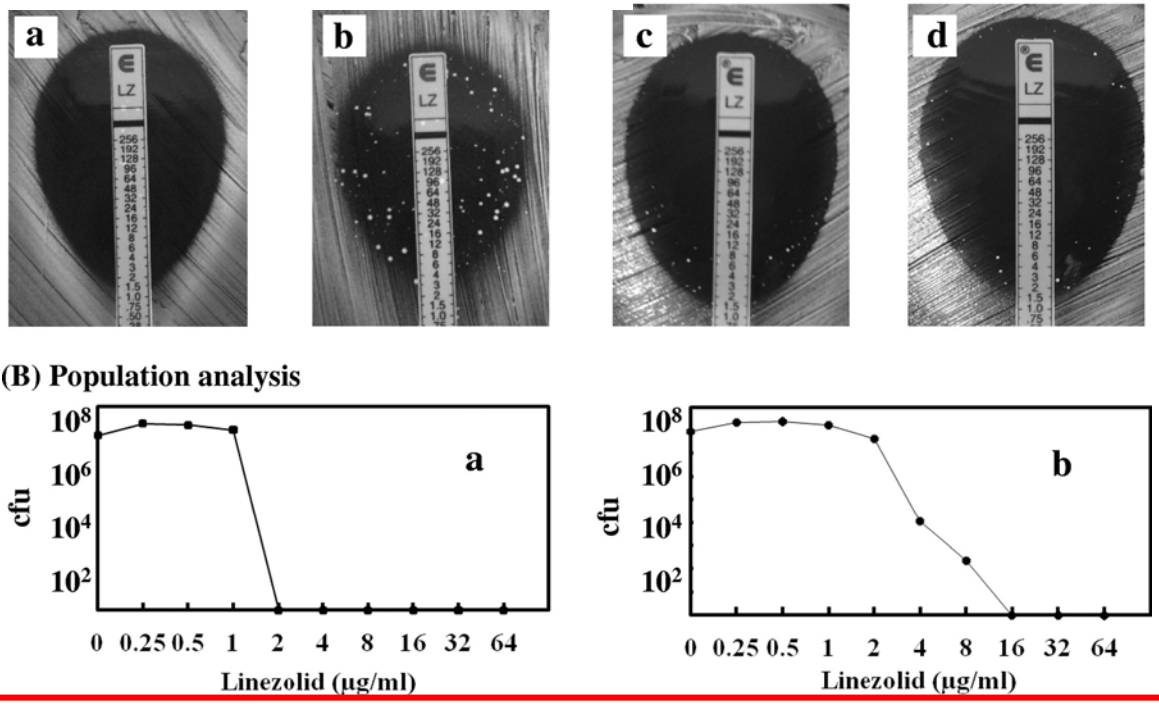
2007:
Resistance to linezolid by mehylation (*cfr*)



Toh et al. Mol Microbiol. 2007;64:1506-14.

The *S. aureus* saga: emergence of linezolid resistance

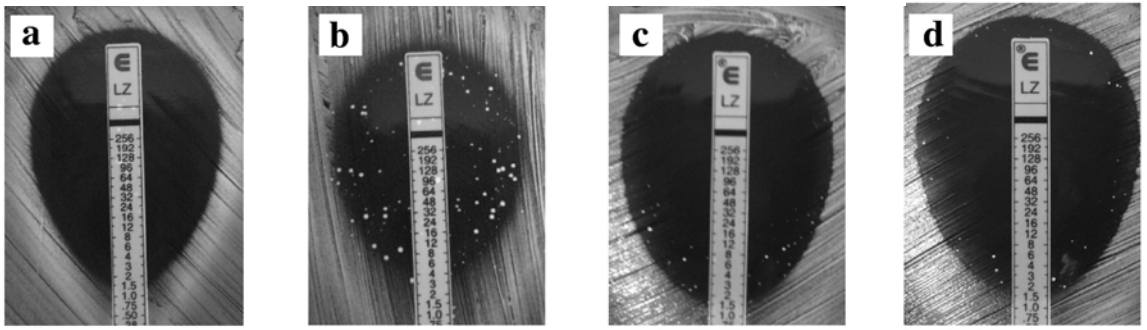
Ribosomal mutations and heteroresistance



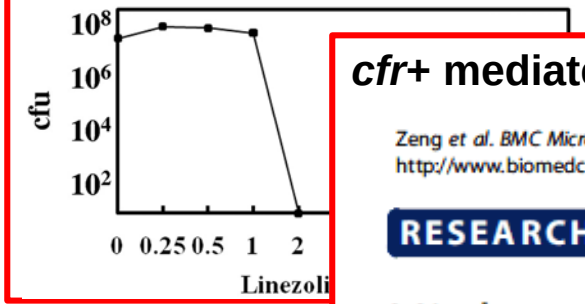
Ikeda-Dantsuji *et al.* Antimicrob Agents Chemother. 2011;55:2466-2468 - PMID 21357291

The *S. aureus* saga: emergence of linezolid resistance

Ribosomal mutations and heteroresistance



(B) Population analysis



Ikeda-Dantsuji *et al.* Antimicr

cfr+ mediated resistance (ribosomal methylation – plasmid mediated)

Zeng *et al. BMC Microbiology* 2014, **14**:151
http://www.biomedcentral.com/1471-2180/14/151

BMC Microbiology

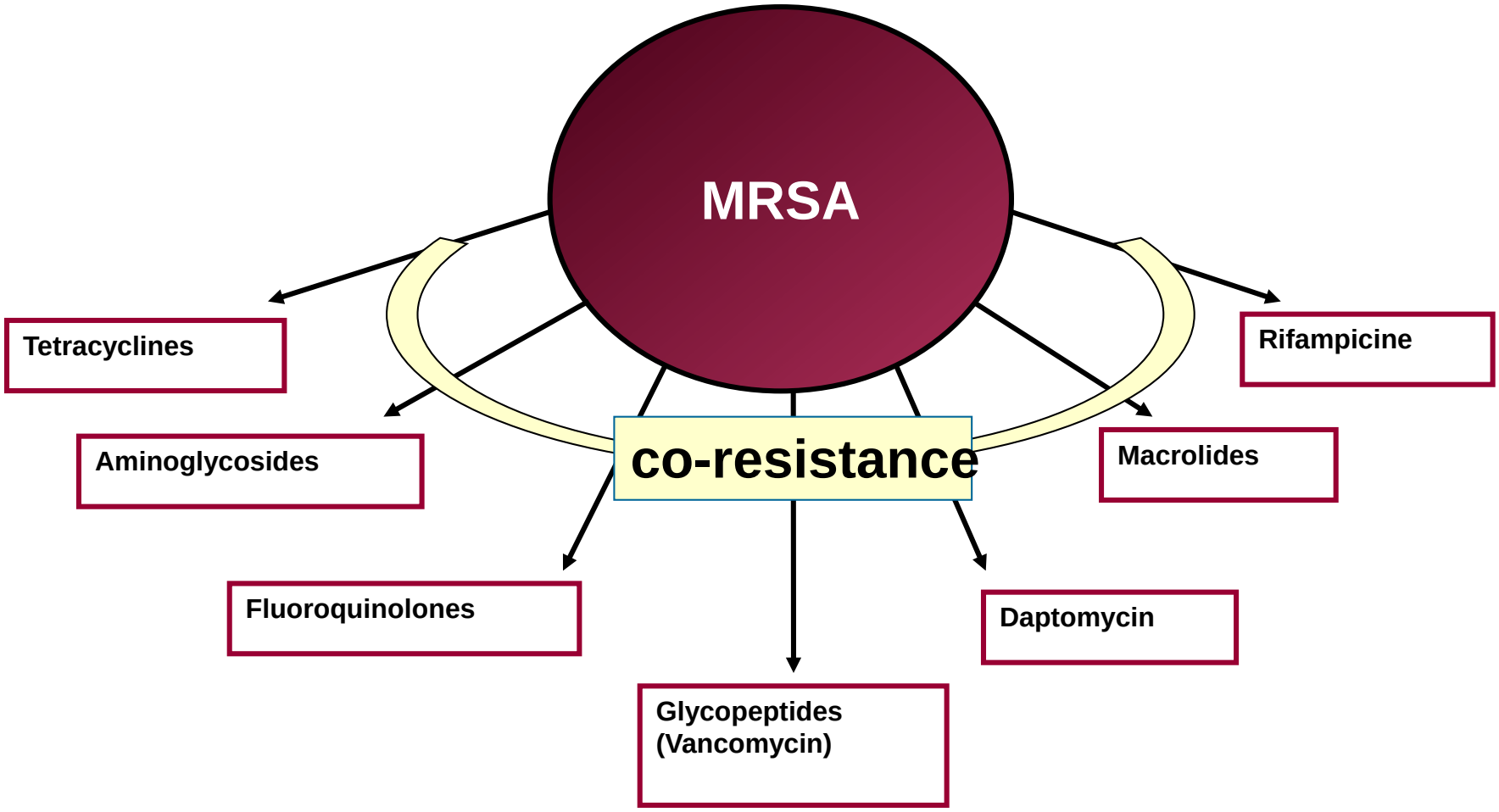
RESEARCH ARTICLE Open Access

High prevalence of Cfr-producing *Staphylococcus* species in retail meat in Guangzhou, China

Zhen-Ling Zeng[1†], Hong-Kun Wei[1†], Jing Wang[1†], Da-Chuan Lin[2], Xiao-Qin Liu[1] and Jian-Hua Liu[1*]

Zeng et al. BMC Microbiol. 2014;14:151 (pages) - PMID 24913069

Warning: Methicillin resistance and co-resistance



+ sélection of strains with decreased susceptibility to other molecules
(linezolid, quinupristin-dalfopristin, ...)

Cantón & Ruiz-Garbajosa Curr Opin Pharmacol. 2011;11:477-485 - PMID 21840259

Methicillin / vancomycin / linezolid non-susceptible *S. aureus*: what wan we do ?

Agent	Dose	Notes
tigecycline	100 mg → 50 mg/q12h	• IV only • dose limited due to tolerance
daptomycin	4 – 6 mg/kg Q24h IV	• bactericidal • doses uncertain (myopathies if ↗)
ceftaroline	600 mg every 12 h IV	• bactericidal • IV only and requires compliance
telavancin oritavancin * dalbavancin *	10 mg/kg qD 1200 mg once 1000 mg + 500 mg at day 7	• bactericidal (VISA and VRSA not susceptible !) • IV only • telavancin: nephrotoxicity and teratogenic risk • convenient use but long infusion time (1-3h) • prolonged tissue accumulation (risk ?)
delafloxacin *	300 mg every 12h IV 450 mg every 12h PO	• bactericidal • efficient IV → oral switch • many severe toxicities in label (black box)
tedizolid *	200 mg qD (IV or oral)	• active against linezolid *cfr*+ resistant strains • efficient IV → oral switch • better tolerance than linezolid

Adapted from the IDSA guidelines (Stevens DL, et al. Clin Infect Dis 2014;59:e10–52 – PMID 24973422.)

* approved after publication of the IDSA guidelines (notes based on analysis of the official US and EU labels [no EU label for delafloxacin])

Streptococcus pneumoniae

Colonies of
S. pneumoniae
CDC Public Health
Image Library
http://phil.cdc.gov/phil

Do we have a problem ?

Obituary

J.-M. Ghuysen

This man discovered the mode of action of penicillin

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

A quick survey of the main (common) bacterial causative organisms

CAP and HCAP	
Outpatient, no sigificant comorbidity	***Streptococcus pneumoniae*** ***Mycoplasma pneumoniae***, *Chlamydophila pneumoniae,* ***Haemophilus influenzae***, *Legionella* spp., *Mycobacterium tuberculosis*, endemic fungi)
Outpatient, comorbities or HCAP with no resistance risk factors	**Drug resistant *Streptococcus pneumoniae* (DRSP)** Enteric Gram-negative; anaerobes (with aspiration)
Inpatient, with comobidities or HCAP with no resistance risk factors	***Streptococcus pneumoniae* (including DRSP)**, ***Haemophilus influenzae***, ***Mycoplasma pneumoniae***, *C. pneumoniae*, *Legionella* spp. Enteric Gram-negatives, anaerobes, others…
Severe CAP, with no risks for *Pseudomonas aeruginosa*	***Streptococcus pneumoniae* (including DRSP)**, ***Haemophilus influenzae***, ***Mycoplasma pneumoniae,*** Legionella spp., ***Staphylococcus aureus*** Gram-negative bacilli, others
Severe CAP, with risks for *P. aeruginosa*, or HCAP with resistance risk factors	All of the above pathogens, plus ***P. aeruginosa***

Infectious Diseases (Cohen, Opal & Powderly, eds), 3d edition, Elsevier 2010,
• Niederman M.: Community-acquired pneumonia (chapter 27))
available on line at http://www.expertconsultbook.com)

Streptococcus pneumoniae resistance

REVIEW ARTICLE

Drugs 2007; 67 (16): 2355-2382
0012-6667/07/0016-2355/$49.95/0

Multidrug-Resistant *Streptococcus pneumoniae* Infections

Current and Future Therapeutic Options

Françoise Van Bambeke,[1] *René R. Reinert,*[2] *Peter C. Appelbaum,*[3] *Paul M. Tulkens*[1] and *Willy E. Peetermans*[4]

1 Unité de Pharmacologie Cellulaire et Moléculaire, Université Catholique de Louvain, Brussels, Belgium
2 Institute for Medical Microbiology, National Reference Center for Streptococci, University Hospital (RWTH), Aachen, Germany
3 Department of Pathology, Hershey Medical Center, Hershey, Pennsylvania, USA
4 Department of Internal Medicine-Infectious Diseases, Katholieke Universiteit Leuven, University Hospital Gasthuisberg, Leuven, Belgium

Van Bambeke F, *et al. Drugs.* 2007;67:2355-82.

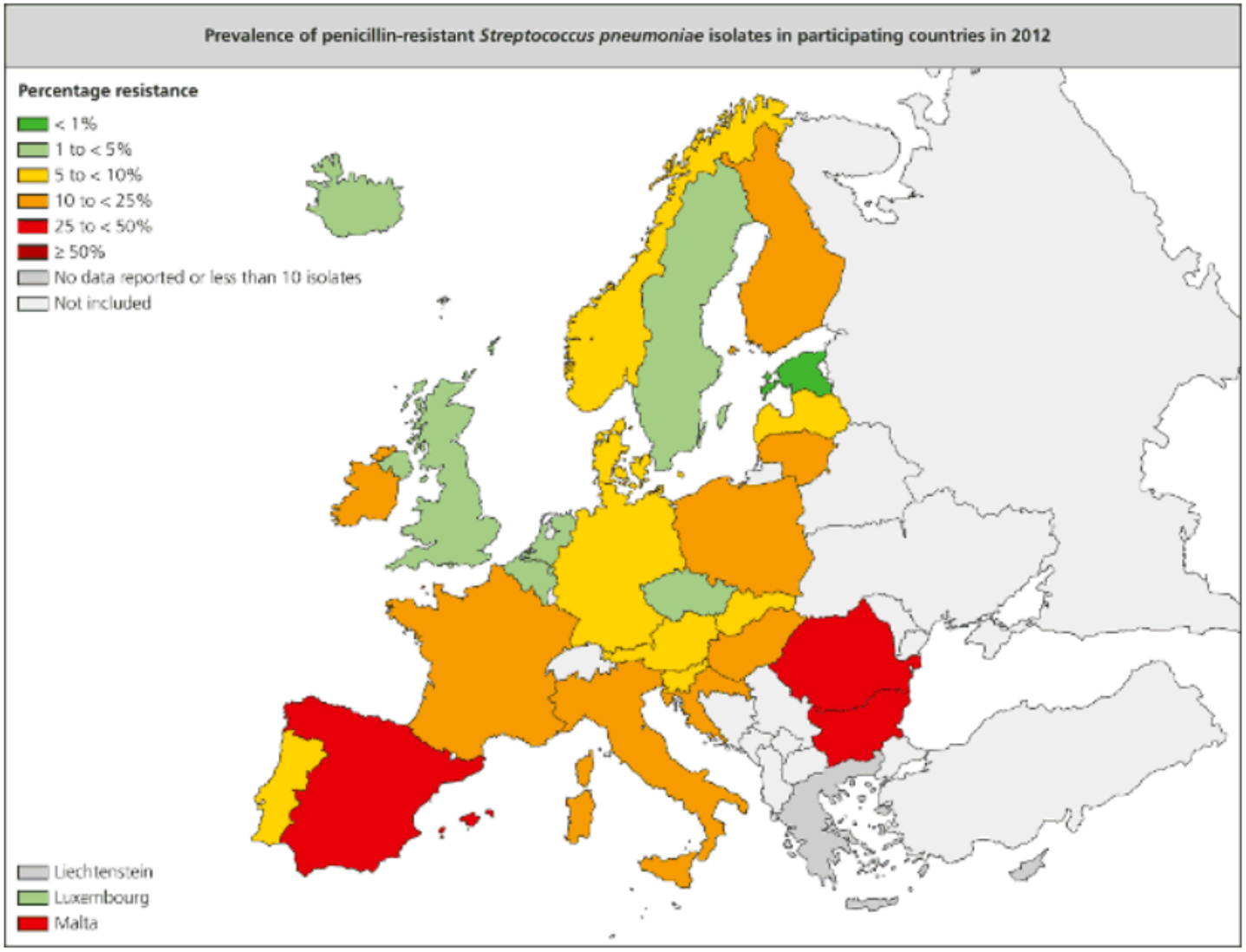
Streptococcus pneumoniae: main mechanisms of resistance

Antibiotic class	Mechanism	Genetic support	Drugs affected	Consequence
β-lactams	↘ Affinity of PNP1a, PBP2x and PBP2b	mosaic genes	all (variable extent)	↘ susceptibility
Macrolides	Methylation of 23S rRNA	*erm(B)*	all except ketolides unless multiple mutations	full resistance
	active efflux	*mef(A)*	14- and 15-membered ring	moderate (?) resistance
Fluoroquinolones	↘ affinity to DNA-gyrase/topisomer-ase complex	point mutations	all (variable extent)	full resistance if several mutations
	active efflux	(*pmrA*) *patA-patB*	gatifloxacin, gemifloxacin [1]	↘ susceptibility
Tetracyclines	ribosomal protection	*tet(A)*, *tet(O)*	all except glycylcyclines	Full resistance
Sulfonamides	↘ of inhibition of dyhydropteroate synthase	repetition of codons for aminoacids	all	Full resistance

[1] also norfloxacin and ciprofloxacin (not recommended)

Adapted from Van Bambeke, *et al*. Drugs. 2007;67:2355-82
See also Lismond, *et a*l. JAC. 2011;66:948-51, Lismond, et al. Intern J Antimicrob Ag. 2012;39:208– 16

Resistance of S. pneumoniae to penicillins: European data

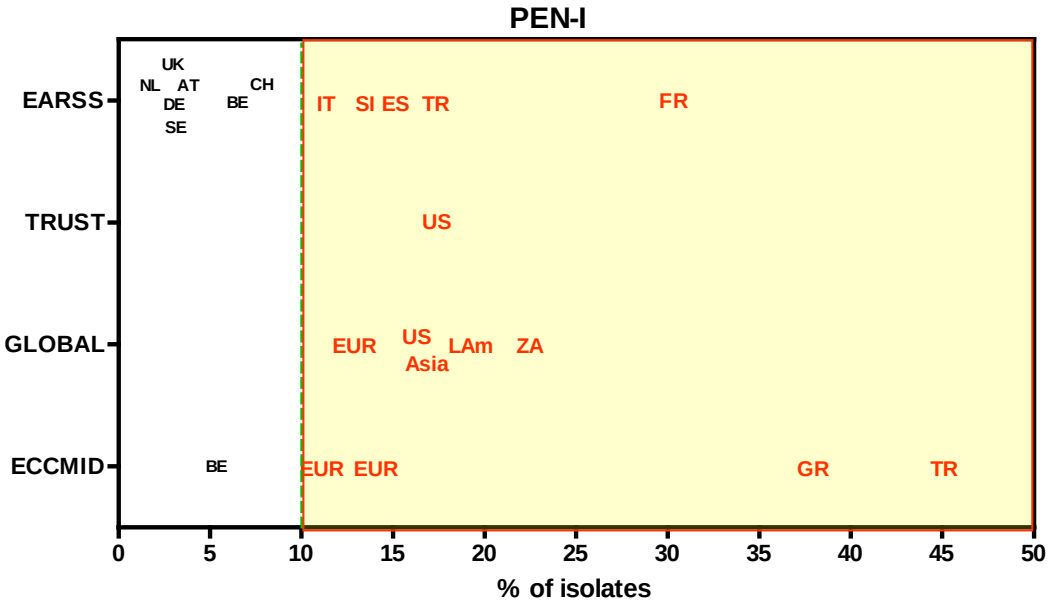


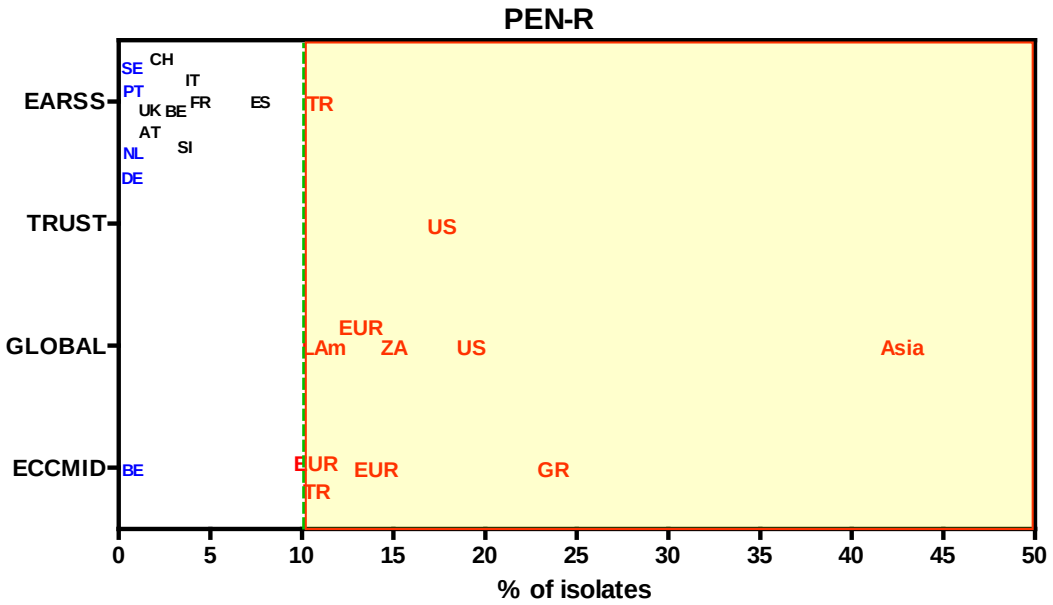
Resistance of *S. pneumoniae* to penicillins *

*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

Most studies used CLSI (non-meningitis) breakpoints





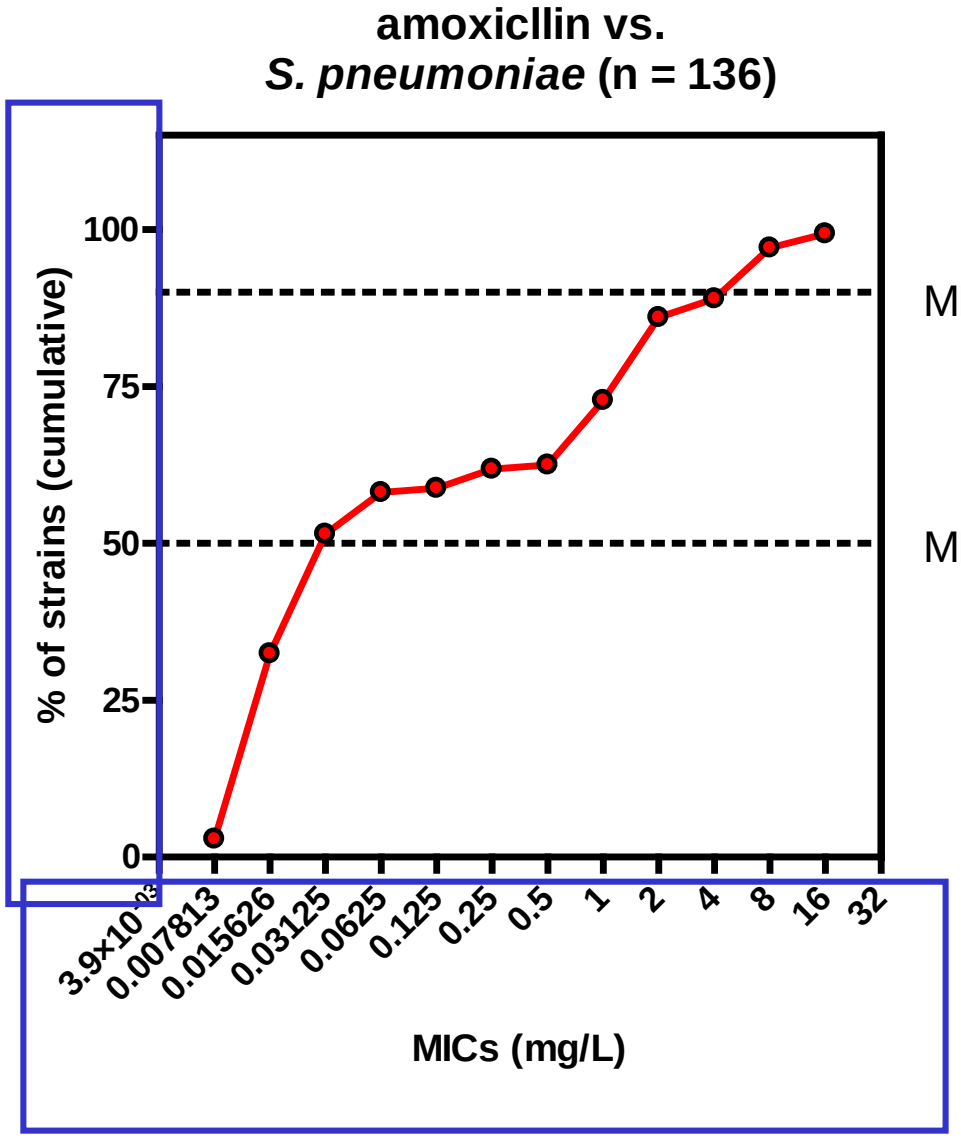
CAP: community acquired pneumonia
CLSI: Clinical and Laboratory Standards Institute (http://clsi.org)

Lismond *et al.*, in preparation

But which breakpoints do we need to use ?

To be honest, I always wondered ...

MIC distribution is a continuous variable…

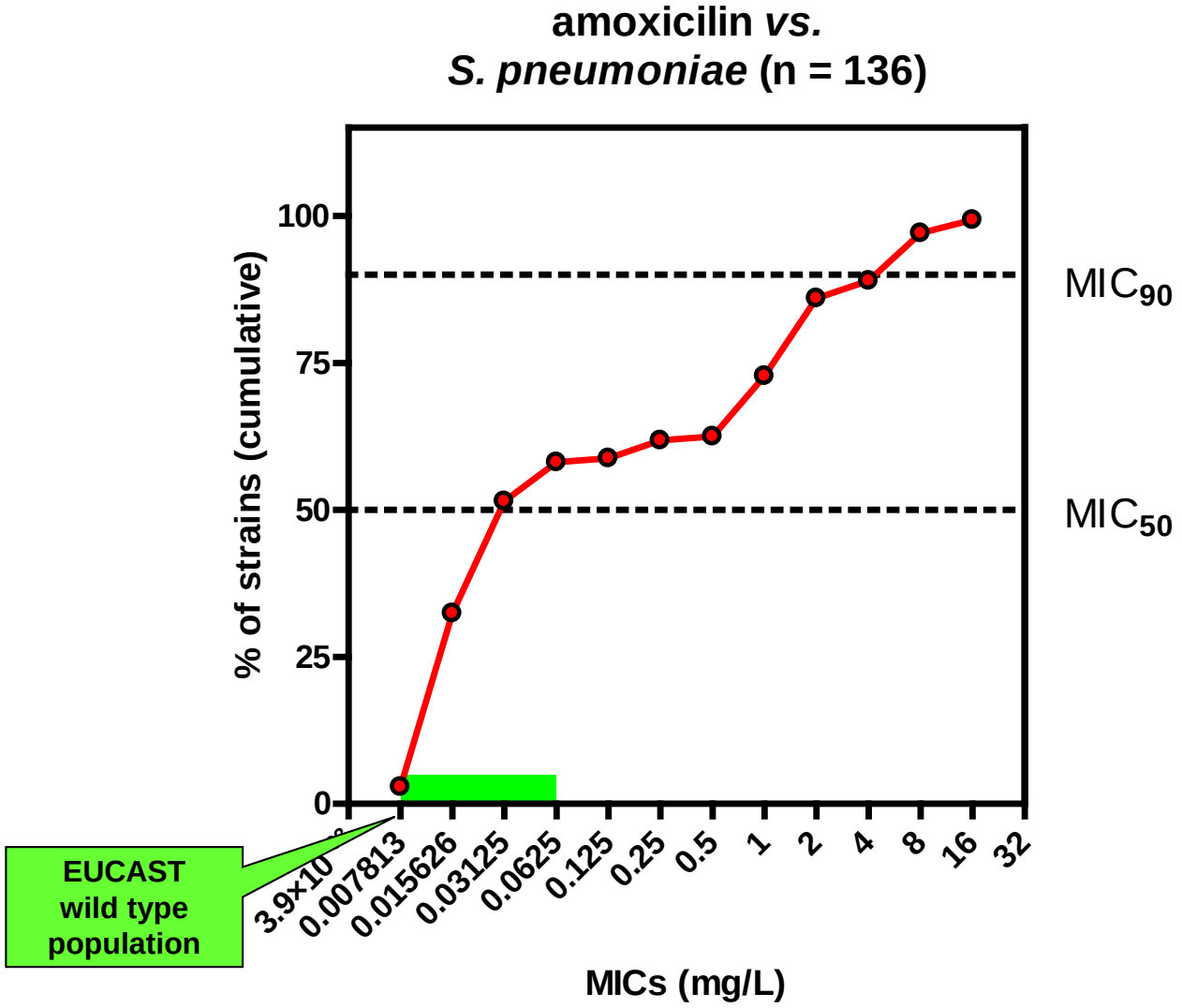


- **Belgian isolates collected between 2009 and 2012 from patients with confirmed cases of CAP**
- **the high MICs of amoxicillin is driven by isolates from patients with past COPD**

Tulkens, unpublished

MIC minimum inhibitory concentration
CAP community-acquired pneumonia
COPD chronic obstructive pulmonary disease

MIC distribution is a continuous variable…



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EUCAST: European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org)
MIC: minimum inhibitory concentration
CAP: community-acquired pneumonia
COPD: chronic obstructive pulmonary disease

Tulkens, unpublished

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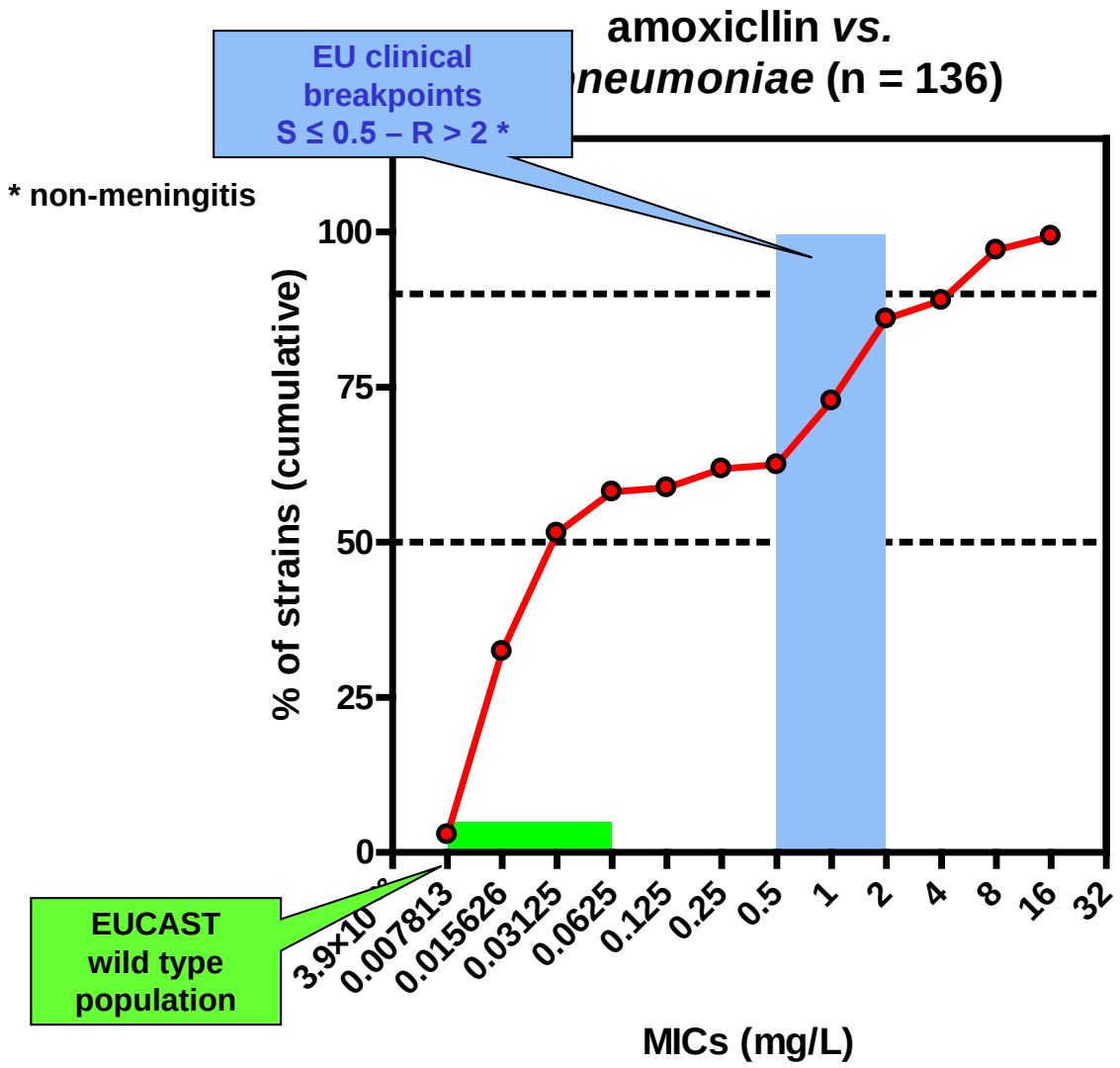

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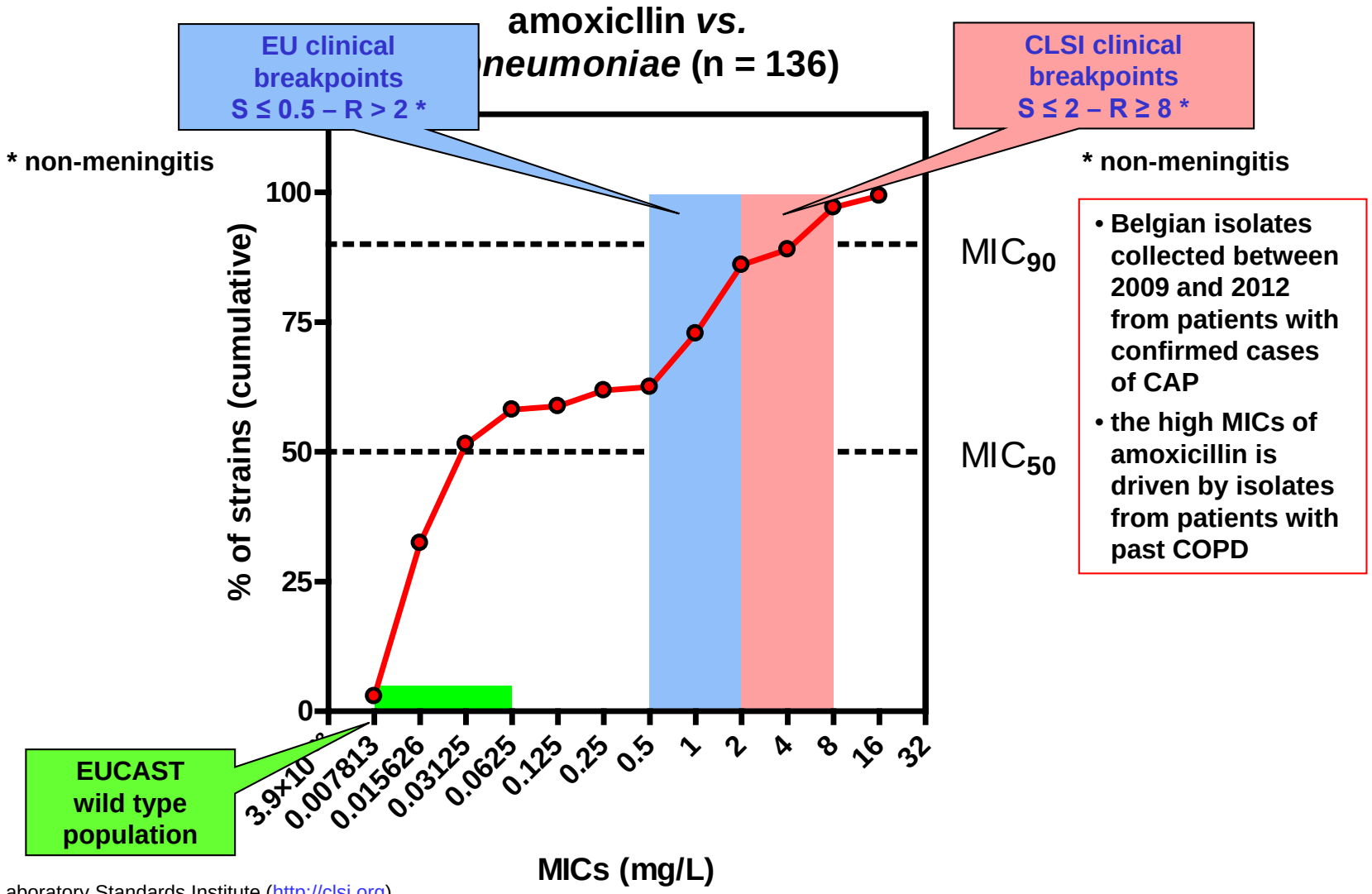

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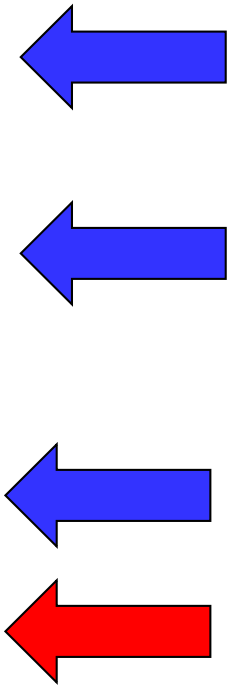
CLSI: Clinical and Laboratory Standards Institute (http://clsi.org)
EUCAST: European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org)
MIC: minimum inhibitory concentration
CAP: community-acquired pneumonia
COPD: chronic obstructive pulmonary disease

Tulkens, unpublished

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

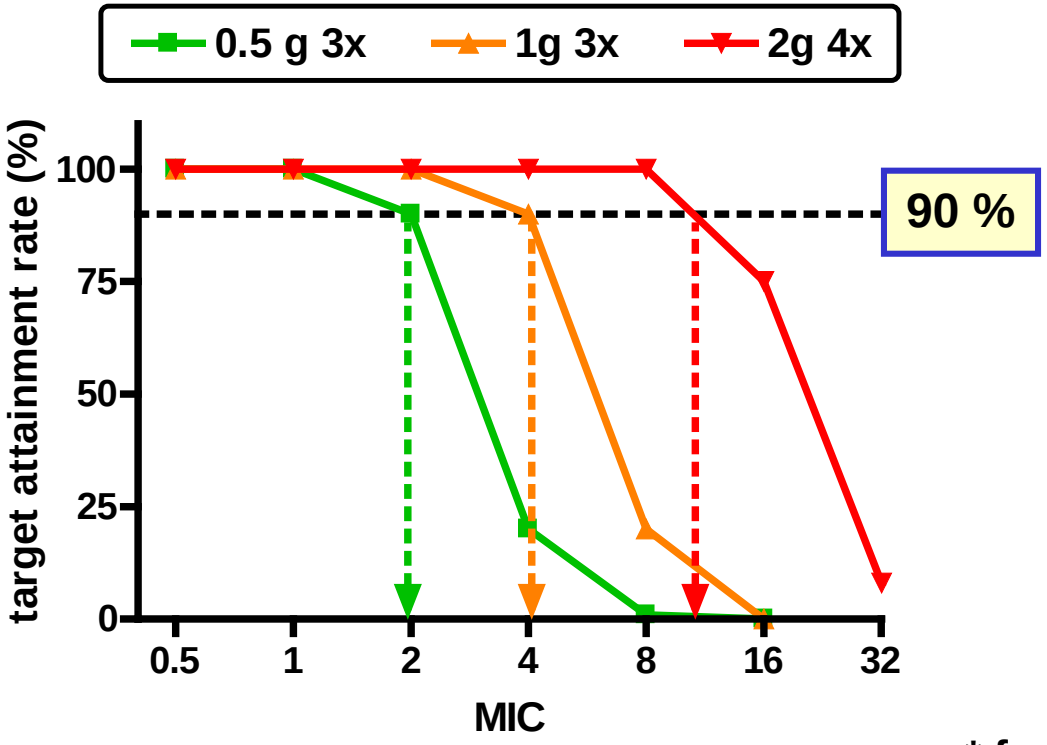
- With the [new] CLSI breakpoint (MIC ≥ 8 mg/L), very few isolates will be defined as resistant….
- In fact, most experts believe that CAP caused by organisms with a penicillin MIC of 4 mg/L or higher (still an uncommon finding), can lead to an increased risk of death.[1]
- For that reason, Europe has set its "R" breakpoint at > 2 mg/L.[2]
- **Dosage adaptation over the original 250 mg BID is necessary for isolates with MIC between 0.25 and 2 mg/L (➔ 0.5 g TID, 1 g TID, or extended-release forms …)**



CLSI: Clinical and Laboratory Standards Institute
EUCAST: European Committee on Antimicrobial Susceptibility Testing
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) (accessed 20/04/2014)

EUCAST calculations of target attainment rate for amoxicillin against *S. pneumoniae*

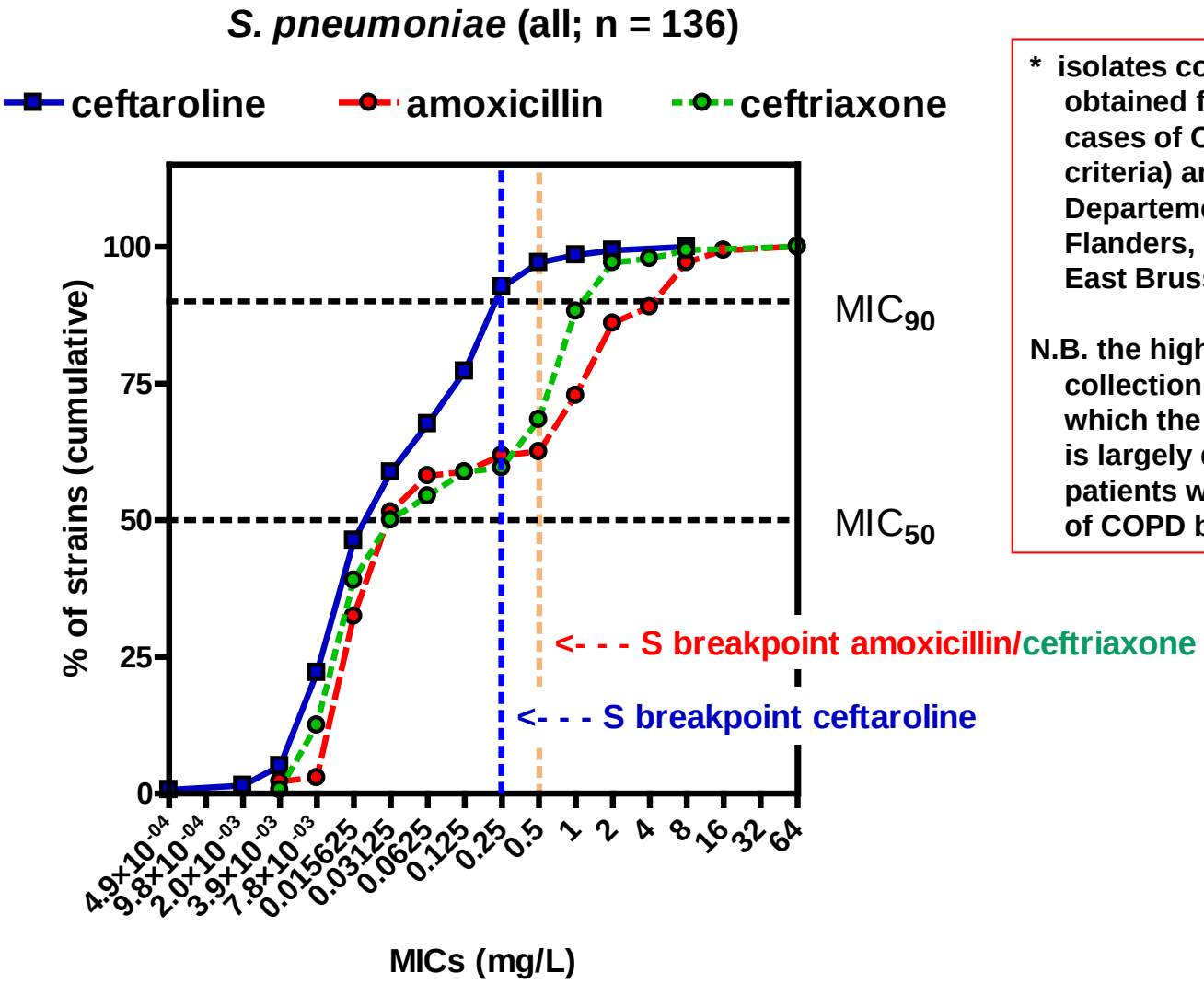


*** for *f* T >MIC = 40%**

By increasing the dose and multiplying the number of daily administration, you may cover bacteria with MIC up to 8 mg/L… but the total daily dose will be very high and

Graph prepared from data in http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Amoxicillin_rationale_Nov2010_v_1.0.pdf

More potent β-lactams may help when amoxicillin fails…



* isolates collected between 2009 and 2012 obtained from patients with confirmed cases of CAP (clinical and radiological criteria) and seen at the Emergency Departement of 4 hospitals (1 in East-Flanders, 1 in North Brussels, 1 in South-East Brussels, 1 in Hainaut)

N.B. the high MICs of amoxicillin in this collection (with 11 % of the strains for which the MIC of amoxicillin is > 2 mg/L) is largely driven by recent isolates from patients who had suffered from episodes of COPD before having contracted a CAP.

Tulkens et al. 26th ICC, 2013 and unpublished

Resistance of *S. pneumoniae* to macrolides and tetracyclines *

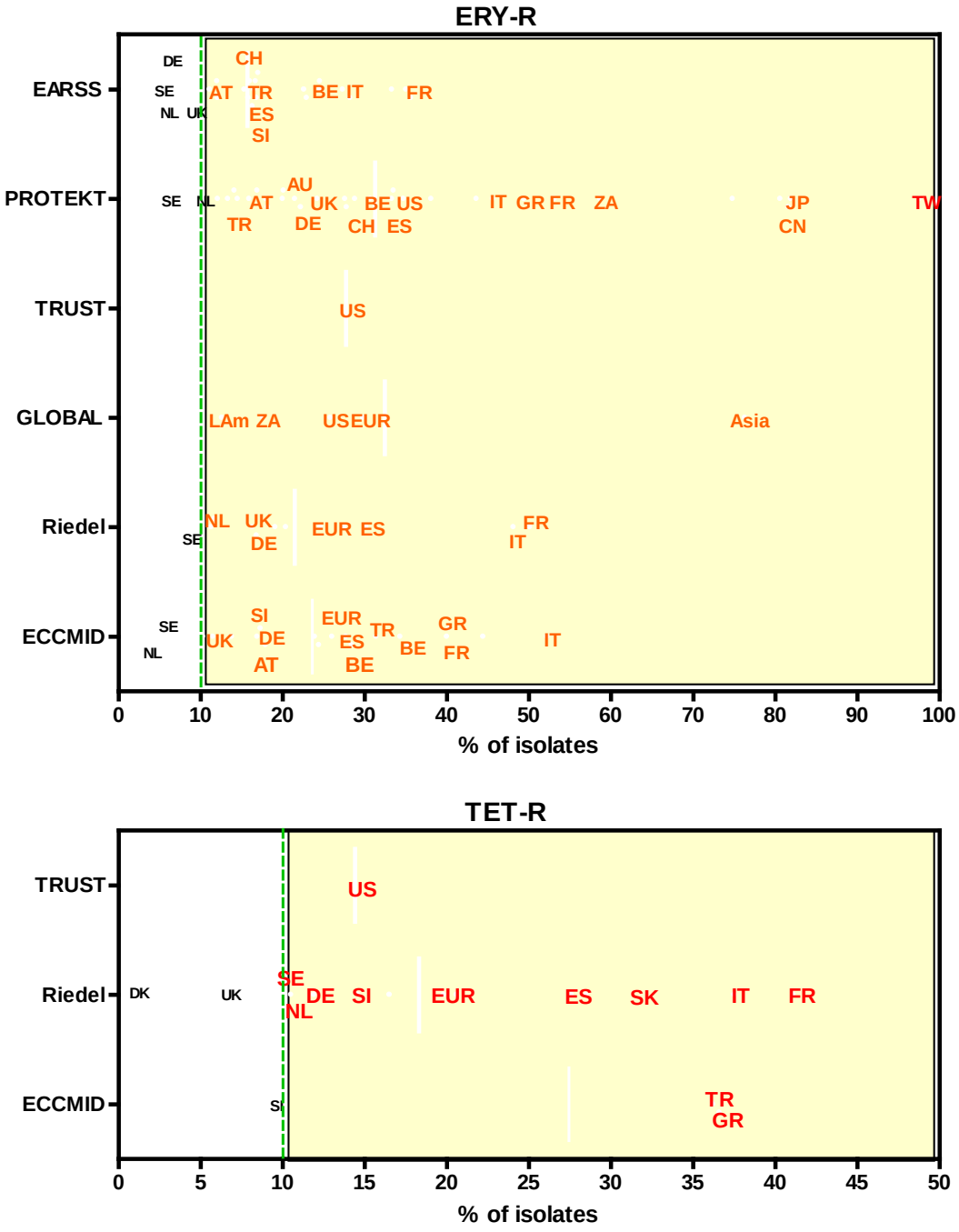
*analysis of resistance to erythromycin and doxycycline (with CAP as main indication) in surveillance systems or publications (*S. pneumoniae*)

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

Most studies used CLSI breakpoints
- erythromycin: S ≤0.25 – R ≥1
- Doxycycline: S ≤0.25 – R ≥1

Lismond *et al.*, in preparation

CAP: community-acquired pneumonia



Are macrolides still useful ?

- not as only agents if resistance rates > 20 % [1]
- but if used in combination with β-lactams to
  - act againts organisms with low susceptibility to β-lactams (*Mycoplasma*, *Chlamydia*, *Legionella*) [2] when these are expected to be present and important (to be discussed)
  - to provide a so-called "antinflammatory activity" (highly discussed [3], but possible development with non-antibiotic derivatives [see next slide]).

1 a value often considered as being a critical threshold in a context of empirical therapy (Limond, *et al. Int J Antimicrob Agents*. 2012;39:208-16)

2 Baum: Mycoplasma and Ureaplasma / Stamm & Bateiger: Chlamydia and Chlamydophila / Edelstein & Cianciotto: Legionella / In Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th edition available on line at https://expertconsult.inkling.com (accessed: 4 April 2014)

3 Spagnolo, *et al. Eur Respir J*. 2013;42:239-51

Anti-inflammatory action of "macrolides" ?

BJP British Journal of Pharmacology

DOI:10.1111/bph.12574
www.brjpharmacol.org

RESEARCH PAPER

Azithromycin analogue CSY0073 attenuates lung inflammation induced by LPS challenge

V Balloy[1,2,3,4], A Deveaux[1,2], D Lebeaux[5], O Tabary[1,2], P le Rouzic[1,2], J M Ghigo[5], P F Busson[6,7], P Y Boëlle[6,7], J Guez Guez[8], U Hahn[8], A Clement[1,2,9], M Chignard[3,4], H Corvol[1,2,9], M Burnet[8] and L Guillot[1,2]

[1]INSERM, UMR_S 938, CDR Saint-Antoine, Paris, France, [2]Sorbonne Universités, UPMC Univ Paris 06, UMR_S 938, CDR Saint-Antoine, Paris, France, [3]Inserm U874, Paris, France, [4]Unité de défense Innée et Inflammation, Institut Pasteur, Paris, France, [5]Unité de Génétique des Biofilms, Institut Pasteur, Paris, France, [6]INSERM, UMR_S 707, Paris, France, [7]Sorbonne Universités, UPMC Univ Paris 06, UMR_S 707, Paris, France, [8]Synovo, Tübingen, Germany, and [9]Pneumologie pédiatrique, APHP, Hôpital Trousseau, Paris, France

Correspondence
Loic Guillot, INSERM, UMR_S 938, 34 rue Crozatier, 75012 Paris, France. E-mail: loic.guillot@inserm.fr

Keywords
macrolides; lung inflammation; cystic fibrosis; COPD

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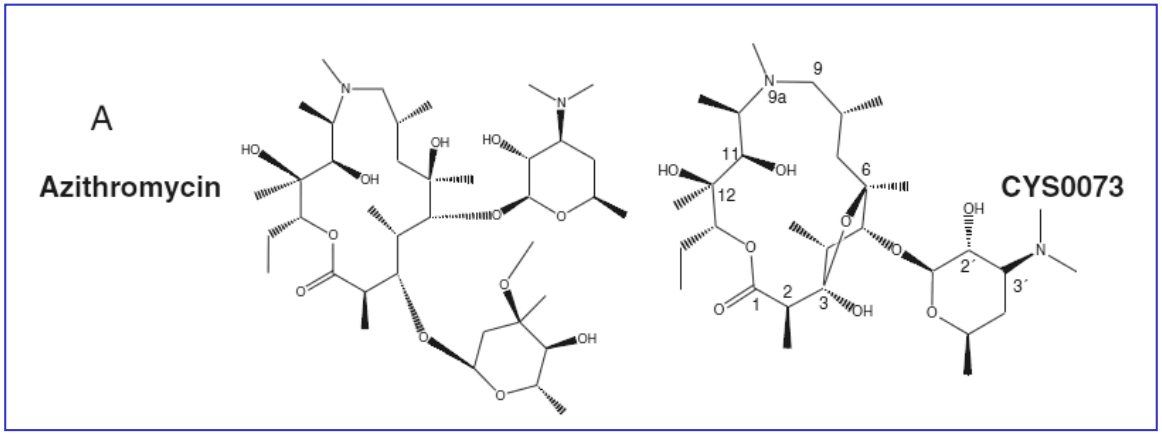
7 January 2014



Mencarelli *et al. Eur J Pharmacol*. 2011;665:29-39

Global Resistance of *S. pneumoniae*: additional information

- Resistance to β-lactams and macrolides may be higher in children[1]
- Global resistance rates in Asia may be worse than currently reported
  - Erythromycin: > 70% of clinical isolates resistant[2]
  - High prevalence of penicillin resistance if using “old” CLSI or EUCAST breakpoints[3]

1. Diekema, *et al. Int. JAC.* 2002;20:412-8 / Brown & Farrell. JAC. 2004;54 Suppl 1:i23-9.2 / Hoban, *et al. Int. J. Infect. Dis*. 2005; 262-273 / Sanchez *et al.* Rev. *Esp. Quimioter*. 2007;20:421-8 / Lee *et* al *Int J Antimicrob Agents*. 2013;42:395-402.
2. Jean & Hsueh. *Int J Antimicrob Agents.* 2011;37:291-5 / Nickerson *et al Lancet Infect Dis* 2009;9:130-5.
3. Song, *et al. Clin Infect Dis* 1999;28:1206-11 / Song *et al Antimicrob Agents Chemother* 2004;48:2101-7 / Mendes *et al Antimicrob Agents Chemother*. 2013;57:5721-6.

Global Resistance of *S. pneumoniae*: additional information

- Resistance to ß-lactams and macrolides may be higher in c
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TABLE 2 Comparative antimicrobial activities of selected agents tested against key Gram-positive pathogens for the APAC region RRS program (2011)

Organism (no. of strains tested) and antimicrobial agent	MIC (μg/ml)			% S/% R[a]	
	50%	90%	Range	CLSI	EUCAST
S. pneumoniae (42)[e]					
Penicillin[f]	≤0.06	4	≤0.06–8	76.2/4.8	66.7/23.8
Amoxicillin-clavulanate	≤1	8	≤1–>8	76.2/21.4	—/—
Ceftriaxone	≤0.06	8	≤0.06–8	78.6/14.3	66.7/14.3
Clindamycin	≤0.25	>2	≤0.25–>2	50.0/50.0	50.0/50.0
Erythromycin	1	>16	≤0.12–>16	47.6/52.4	47.6/52.4
Levofloxacin	1	1	0.5–2	100.0/0.0	100.0/0.0

APAC: Asisa/Pacific [Australia, Hong Kong, India, Indonesia, Japan, South Korea, Malaysia, New Zealand, Philippines, Singapore, Taiwan, Thailand
RRS: Regional Resistance Surveillance programme

1. Diekema, *et al. Int. JAC.* 2002;20:412-8 / Brown & Farrell. JAC. 2004;54 Suppl 1:i23-9.2 / Hoban, *et al. Int. J. Infect. Dis*. 2005; 262-273 / Sanchez *et al.* Rev. *Esp. Quimioter*. 2007;20:421-8 / Lee *et* al *Int J Antimicrob Agents*. 2013;42:395-402.
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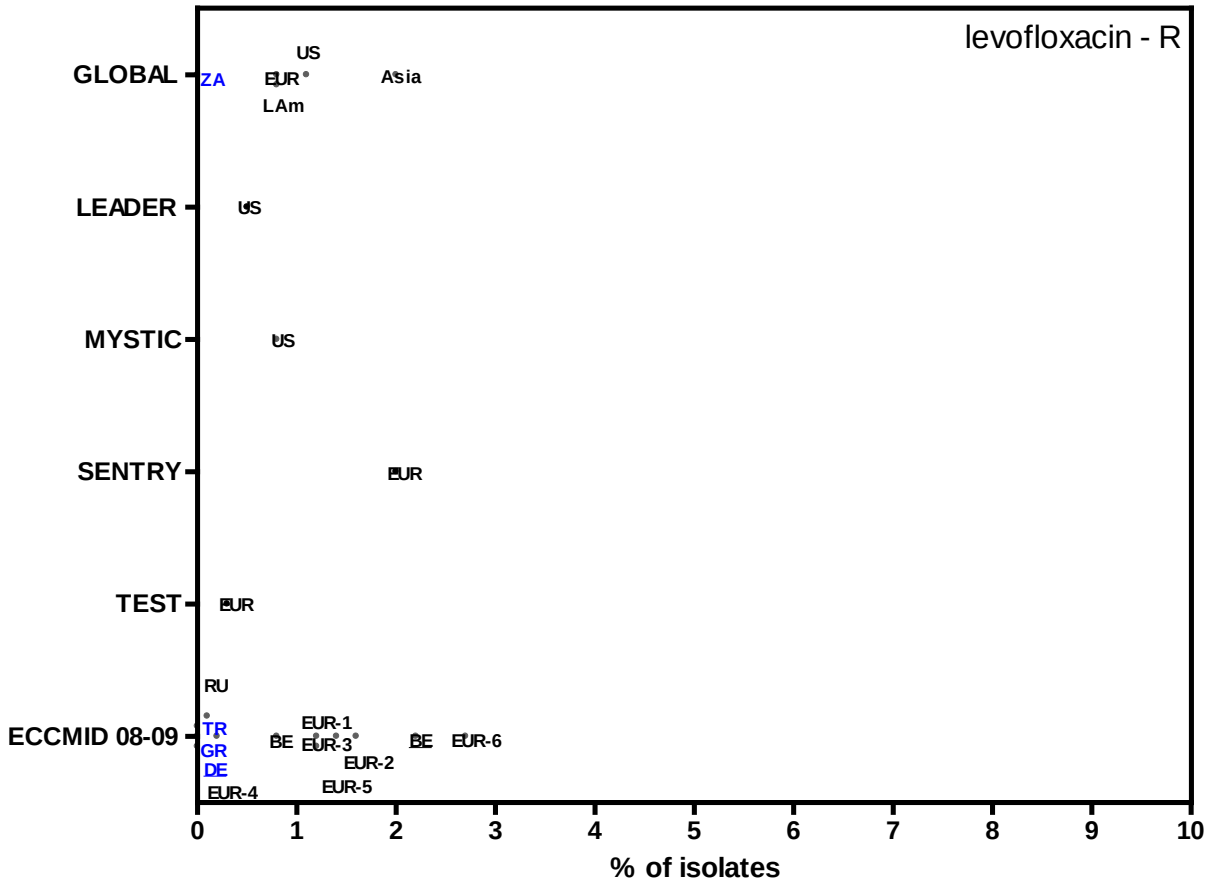
Resistance of *S. pneumoniae* to fluroquinolones

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

- **GLOBAL:** Global Landscape On the Bactericidal Activity of Levofloxacin
- **LEADER:** Linezolid Surveillance Program
- **MYSTIC:** Meropenem Yearly Susceptibility Test Information Collection
- **SENTRY:** Antimicrobial Surveillance Program (2005–2006)
- **TEST:** Tigecyline Evaluation Surveillance Trial
- **ECCMID 08-09** : abstracts of the 18th and 19th European Congresses of Clinical Microbiology and Infectious Diseases

Most studies used CLSI breakpoints

- levofloxacin: S ≤2 – R ≥8
- doxycycline: S ≤1 – R ≥4



Lismond *et al.*, in preparation

CAP: community-acquired pneumonia

Resistance of *S. pneumoniae* to fluoroquinolones

- Several countries noted no or little resistance over time if used appropriately even with relatively large use

Example #1: Canada

Table 1. *In vitro* activities of fluoroquinolones against selected pathogens in the CANWARD study 2007–11 as well as prevalence of MDR isolates involving fluoroquinolone over time

	Year				
Organism/resistance phenotype	2007	2008	2009	2010	2011
S. pneumoniae					
% R[a] levofloxacin (no. of isolates tested)	0.3 (591)	1.5 (514)	0 (129)	0.6 (168)	0 (138)
% MDR[b]	3.2	6.8	3.9	7.1	7.2
% MDR isolates resistant to levofloxacin	5.3	11.4	0	8.3	0

[a]R includes both intermediate and resistant isolates.
[b]MDR includes both intermediate and resistant isolates for the following agents for the following organisms: *E. coli*, *K. pneumoniae* and *E. cloacae* (ciprofloxacin, ceftriaxone, meropenem, piperacillin/tazobactam, trimethoprim/sulfamethoxazole and gentamicin); *P. aeruginosa* (ciprofloxacin, ceftazidime, meropenem, piperacillin/tazobactam and gentamicin); *S. aureus* (ciprofloxacin, clarithromycin, oxacillin and trimethoprim/sulfamethoxazole); and *S. pneumoniae* (levofloxacin, penicillin, clarithromycin and trimethoprim/sulfamethoxazole).

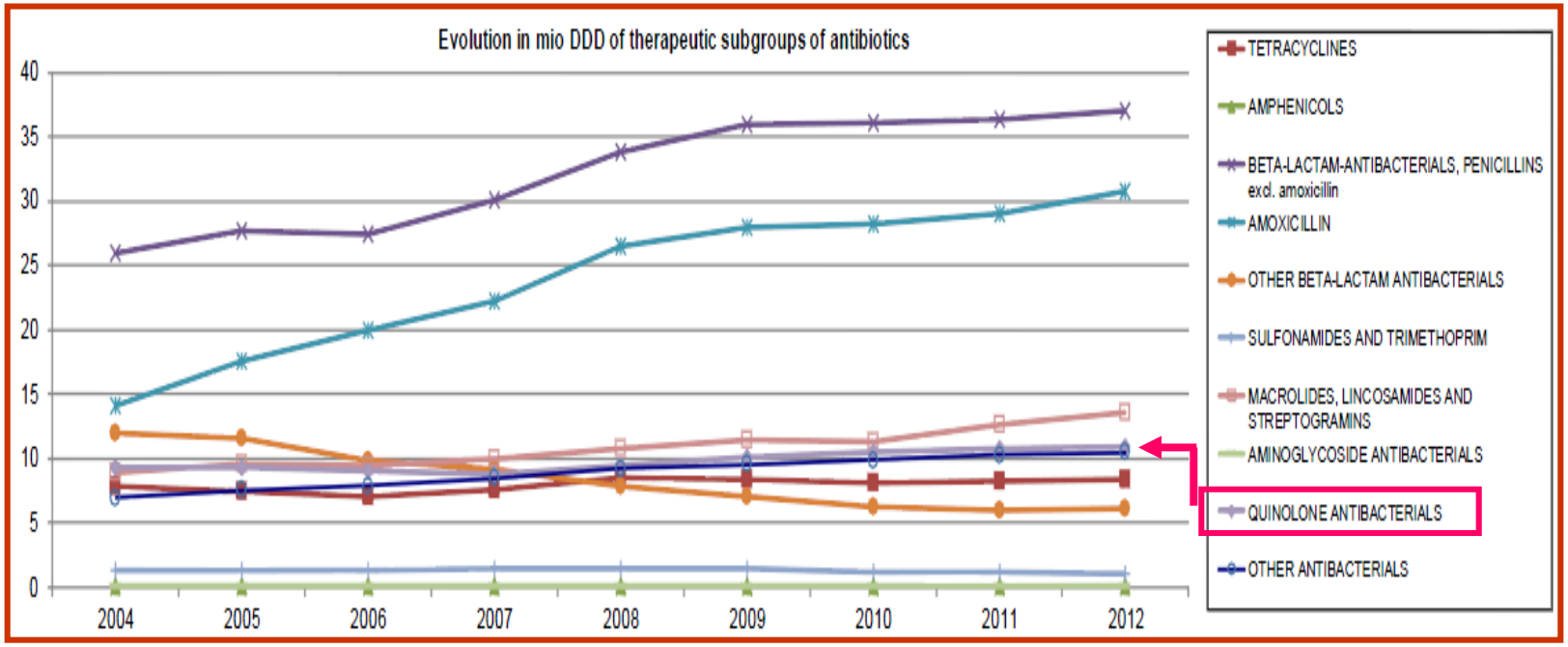
Karlowski, *et al. JAC*. 2013;68(Suppl 1): i39–i46

Resistance of *S. pneumoniae* to fluoroquinolones

- Several countries noted no or little resistance over time if used appropriately even in relatively large use

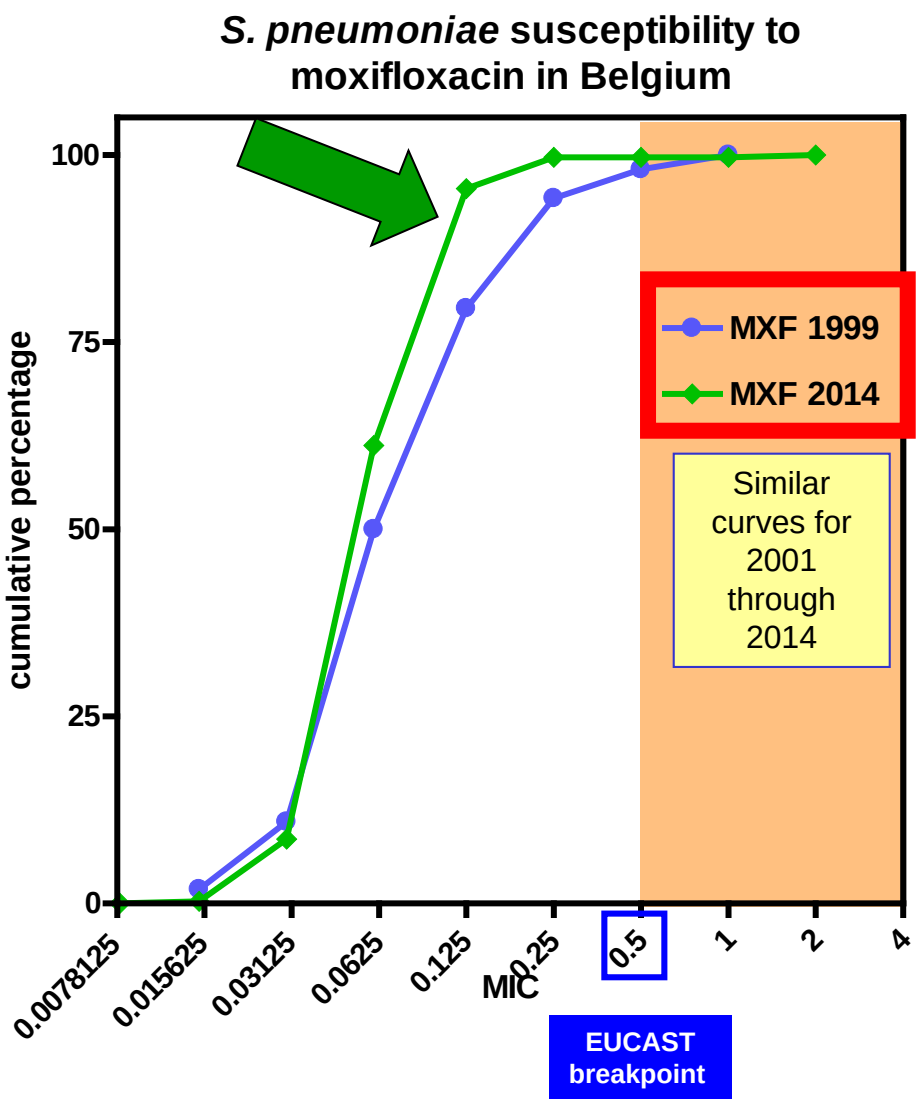
Example #2: Belgium

Antibiotics used in the ambulatory care in Belgium (reimbursement data [>95% of total use])



Source: Belgian National Institute for Sickness and Invalidity Insurance:"*Tableaux de bord pharmaceutiques: Délivrances pharmaceutiques dans le secteur ambulant* – année 2012"
http://www.inami.be/drug/fr/statistics-scientific-information/pharmanet/pharmaceutical-tables/pdf/2012/tables2012.pdf
Last accessed: 20/01/2014

Has resistance to moxifloxacin materialized: evidence for *S. pneumoniae* in Belgium from 1999 to 2014 *



*** Moxifloxacin was introduced in Belgiumin 2001 and became the almost only fluoroquinolone used for RTI since 2004**

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 at http://bacterio.wiv-isp.be/other-activities/Streptococcus%20pneumoniae

Vanhoof *et al*. 19th ECCMID, Helsinki, 2009
Ceyssens *et al*. 35th RICAI, Paris, 2015
Ceyssens et al. PLoS One. 2016;11:e0154816 - PMID 27227336

Resistance of *S. pneumoniae* to fluoroquinolones

- The situation may be different in other countries (Asia)
  - 4% resistance to levofloxacin for PNRSP in China [1]
  - 8.6 % (6/70) in adults in China [2]
  - 4.7 % in Asian Countries (all cases from Korea, Hong-Kong, Taiwan) in association with previous treatment with fluoroquinolones, cerebrovascular disease, and healthcare-associated infection [3]

PNRSP: penicillin resistant *Streptococus pneumoniae*

1. Jones RN, *et al. Diagn Microbiol Infect Dis*. 2013;77:258-66
2. Guo Q, et al. *Eur J Clin Microbiol Infect Dis* 2014;33:465–70
3. Kang CI, et al. Eur J Clin Microbiol Infect Dis. 2014;33:55-9

Resistance of *S. pneumoniae* to fluoroquinolones

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    fluoroquinolo
    associated i

Table 2 Independent risk factors associated with pneumonia caused by levofloxacin-nonsusceptible *S. pneumoniae*

Variables	Adjusted OR (95 % CI)	*P*
Previous treatment with fluoroquinolone	3.22 (1.05–9.85)	0.041
Cerebrovascular disease	2.88 (1.36–6.06)	0.005
Healthcare-associated infection	2.28 (1.14–4.55)	0.019

Kang et al. Eur J Clin Microbiol Infect Dis. 2014;33:55-9

1. Jones RN, *et al. Diagn Microbiol Infect Dis*. 2013;77:258-66
2. Guo Q, et al. *Eur J Clin Microbiol Infect Dis* 2014;33:465–70
3. Kang CI, et al. Eur J Clin Microbiol Infect Dis. 2014;33:55-9

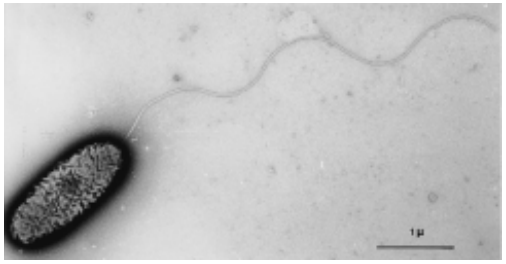
Resistant *S. pneumoniae*: what can we do ?

1. Vaccination
   effective against the serotypes covered but slow drift of resistance to not covered serotypes…[1]

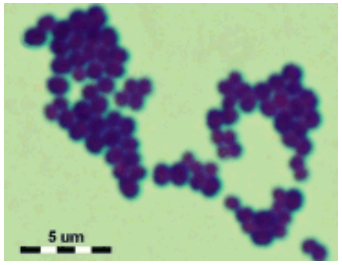
2. Existing antibiotics
   - β-lactams: use higher doses or more potent molecules (and avoid non-conform generics) [a,b]
   - macrolides: to be forgotten in monotherapy [a,c]
   - fluoroquinolones: aim at the most potent (moxifloxacin…) and avoid the marginal ones (levofloxacin) [a]
   - tetracyclines: often high resistance levels (check locally) [d]
   - clindamycin, trimethoprim/sulfamethoxazole: check locally [d]
   - vancomycin, linezolid, tigecycline, lipoglycopeptides, daptomycin, streptogramins: low levels of resistance but poorly documented (because not first line antibiotics) [d]

1 Kaplan et al. Pediatrics 2010;125:429-436 - PMID 20176669 / Pelkonen et al. Emerg Infect Dis 2013;19:1041-1048 - PMID 23777752
a see slides in this presentation
b see presentation on generics
c telithromycin and solithromycin aer active againts macrolide-resistant strains but are facing toxicity (liver) issues (see FDA web site)
d not illustrated here

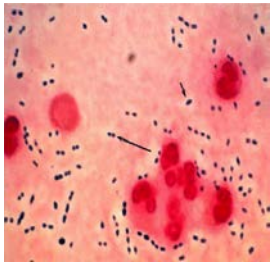
Do we have a conclusion ?



Difficult and in need of major investments



Some good hopes but remain alert !



Less critical … but wait for the next problem !

I could only give an overview…

But, ask questions…