Susceptibility trends in pneumonia pathogens and current prescribing.

Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology & Center for Clinical Pharmacy

Louvain Drug Research Institute,

Université catholique de Louvain

Brussels, Belgium

24th ECCMID Barcelona, Spain 10 – 13 May 2014

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Session: Optimising diagnosis and appropriate antibiotic prescribing in pneumonia

With approval of the Belgian Common Ethical Healthplatform – visa no. V1/14/04/30/060865

Disclosures

Financial support from

- the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
- *Université catholique de Louvain* for past personal support
- Commercial Relationships:
  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …
- Other relationships in relation to this talk
  - Belgian Antibiotic Policy Coordination Committee,
  - European Medicines Agency (as expert for the agency and for Industry)

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 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

Which problem ?

- **Community-acquired pneumonia (CAP):**
  - remains a major acute cause of death (6th in patients > 65 y);
  - *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)
  - Resistance to "older" antibiotics is growing …
- **Hospital/Health Care-acquired/Ventilator associated pneumonia (HCAP/HAP/VAP)**
  - 2nd most frequent acquired infection in the hospital
  - carries a still higher mortality burden (13-55 %)
  - can be caused by a larger variety of organisms highly influenced by prior exposure to antibiotics, type of patient and comorbidities
  - Enteric Gram (-), *S. aureus*, and *P. aeruginosa* are predominant with resistance increasing if late onset (hospital strains)

Infectious Diseases (Cohen, Opal & Powderly, eds), 3d edition, Elsevier 2010,
- Niederman M.: Community-acquired pneumonia (chapter 27)
- Papazian L & Donati SY: Hospital-acquired pneumonia (chapter 28)

available on line at http://www.expertconsultbook.com (last access: 18-03-2014)

BUT…

- **Community-acquired pneumonia (CAP):**
  - remains a major acute cause of death (6th in patients > 65 y);
  - *Streptococcus pneumoniae* is the most commonly identified pathogen, but other bacteria and the atypical pathogens (the causative [illegible] diseases)
  - Resistance to "older" antibiotics is growing …
- **Hospital/Health Care-acquired/Ventilator associated pneumonia (HCAP/HAP/VAP):**
  - 2d most frequent acquired infection in the hospital
  - carries a still higher mortality burden (13-55 %)
  - can be caused by a larger variety of organisms highly influenced by prior exposure to antibiotics, type of patient and comorbidities
  - Enteric Gram (-), *S. aureus*, and *P. aeruginosa* are predominant with resistance increasing if late onset (hospital strains)

Those categorical differences are now blurring…

Woodhead M. *Thorax*. 2013;68:985-6.
Quartin AA, *et al. BMC Infectious Diseases.* 2013,13:561

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)

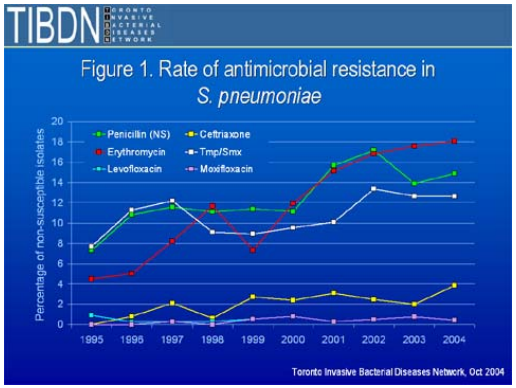
A quick survey of the main (common) bacterial causative organisms

HAP	
Early pneumonia	***Streptococcus pneumoniae*** ***Haemophilus influenzae***, **Methicillin-sensitive *Staphylococcus aureus* (MSSA)** Escherichia coli and non-resistant EGNB,
Late pneumonia	***Pseudomonas aeruginosa*** *Acinetobacter* spp., **Antibiotic-resistant *Enterobacteriaceae***, **Methicillin-resistant *Staphylococcus aureus* (MRSA)**
Other situations	Coagulase-negative *staphylococci*
	Neisseria spp., *Moraxella* spp. *Enterobacter* spp., *Proteus* spp. *Burkholderia cepacia* *Acinetobacter* spp. *Stenotrophomonas maltophilia*
	Anaerobes (*Peptostreptococcus*, Veillonelia, *Bacteroides* spp. *Fusobacterium* spp., *Prevotella* spp., *Actinomyces* spp.
	Intracellular (*Legionella* spp. *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*)

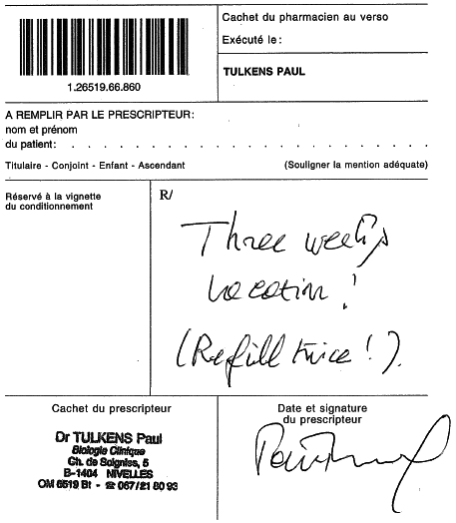
Infectious Diseases (Cohen, Opal & Powderly, eds), 3d edition, Elsevier 2010,
• Papazian L & Donati SY: Hospital-acquired pneumonia (chapter 28)
available on line at http://www.expertconsultbook.com (last access: 18-03-2014)

What is my goal ?

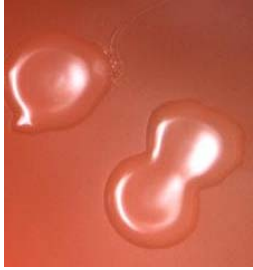
- Discuss with you the trends of resistance of some of these organisms
- how it may impact on you prescription habits…
- leaving to the next speakers the discussion of guidelines …



http://microbiology.mtsinai.on.ca/tibdn/data/arspneumo.asp
Last accessed: 19 March 2014



Streptococcus pneumoniae



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

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)

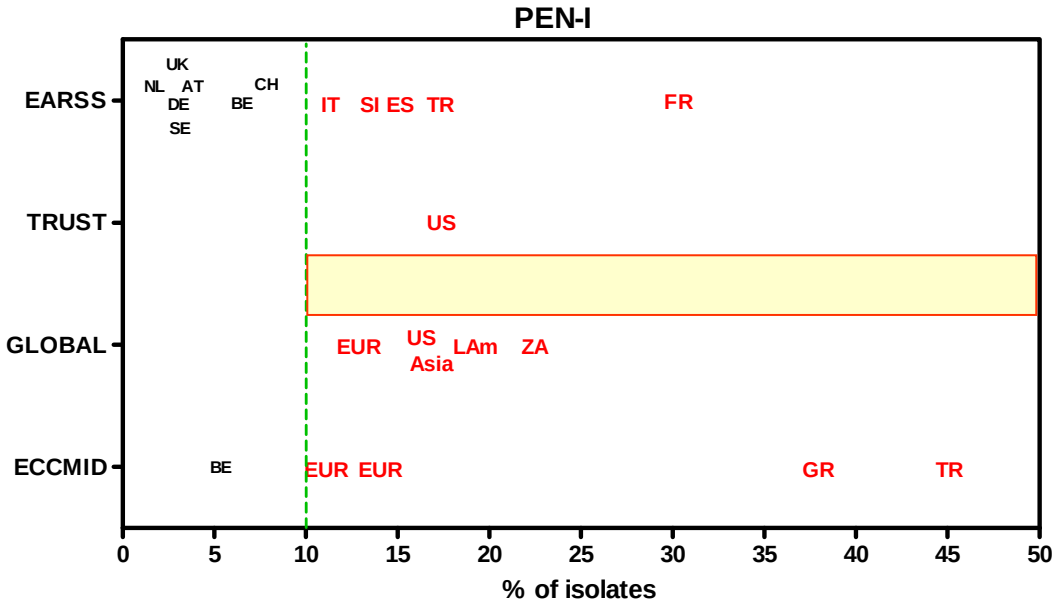
Adapted from Van Bambeke, *et al*. Drugs. 2007;67:2355-82
See also Lismond, *et a*l. JAC. 2011;66:948-51, Lismond, et al. Intern J Antimicrob Ag. 2012;39:208– 16

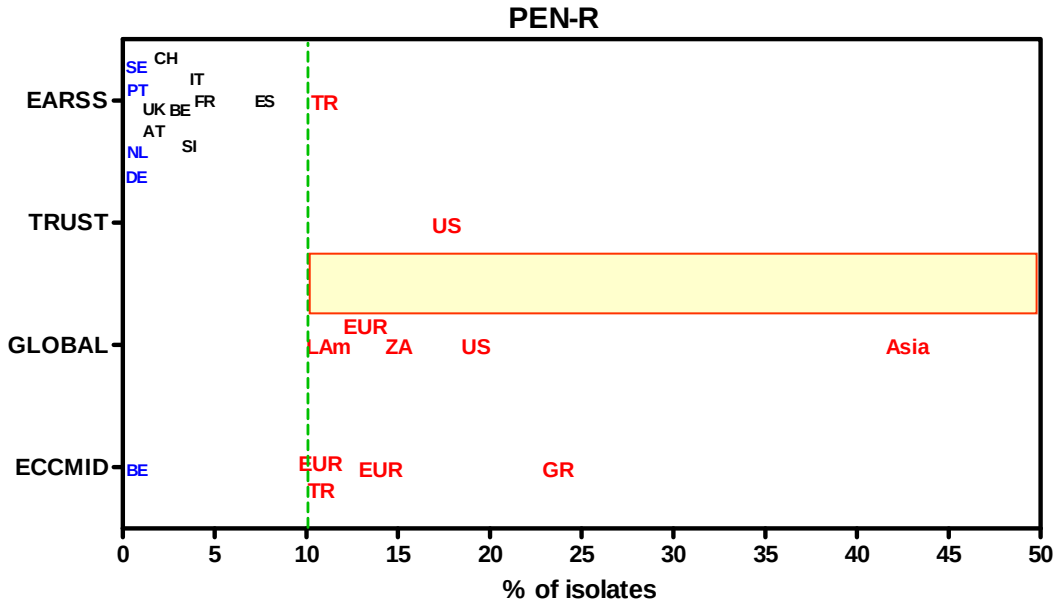
Resistance of *S. pneumoniae* to penicillins *

*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





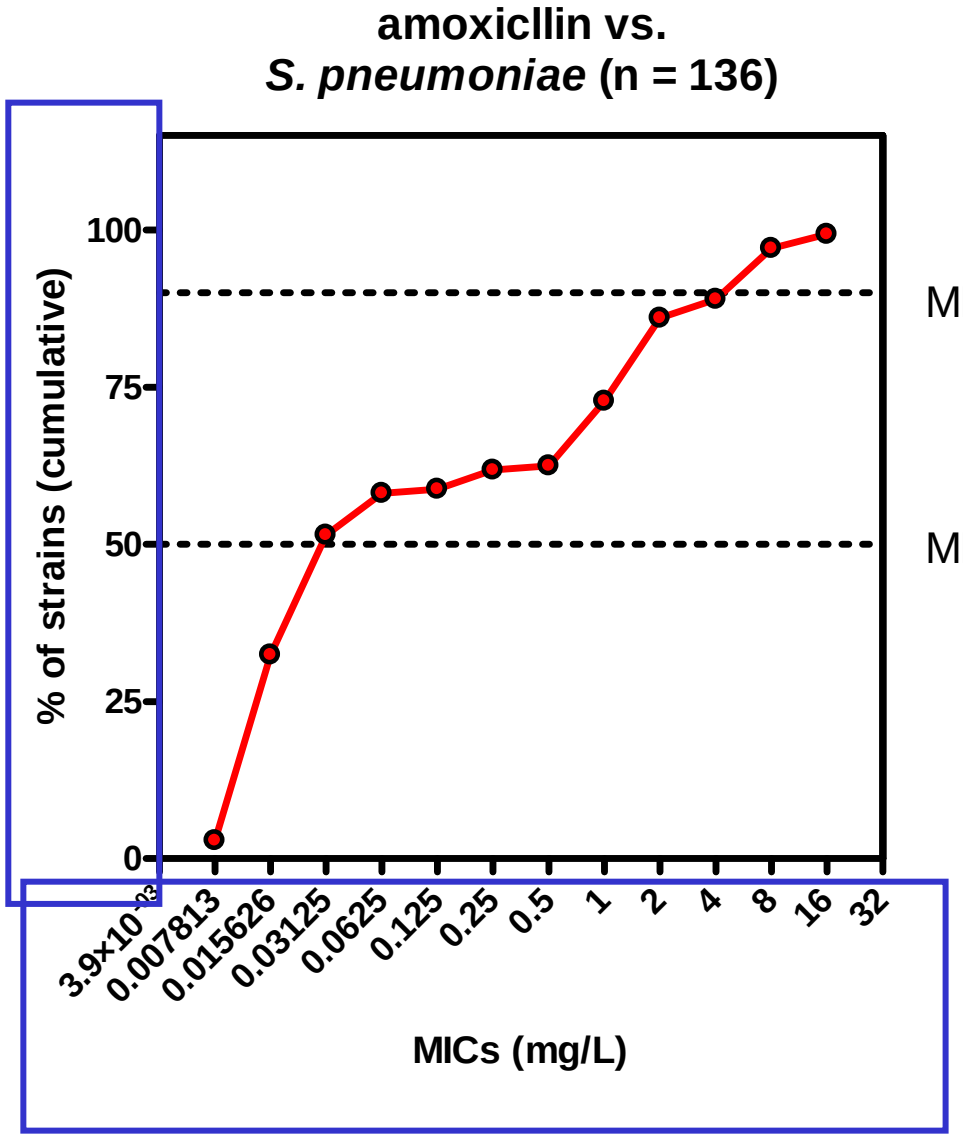
CAP: community acquired pneumonia
CLSI: Clinical and Laboratory Standards Institute (http://clsi.org)

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…



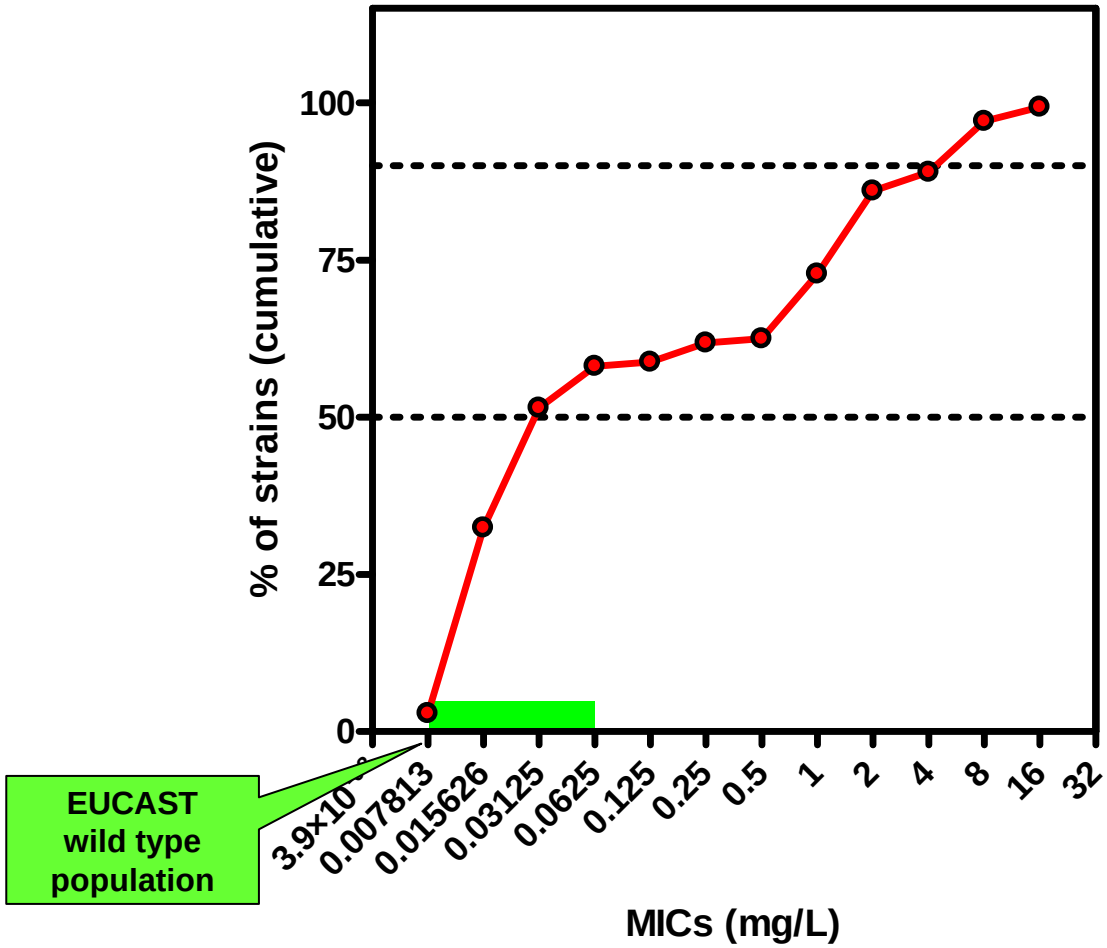
- **Belgian isolates collected between 2009 and 2012 from patients with confirmed cases of CAP**
- **the high MICs of amoxicillin is driven by isolates from patients with past COPD**

Tulkens, unpublished

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

MIC distribution is a continuous variable…

amoxicilin *vs.*
***S. pneumoniae* (n = 136)**

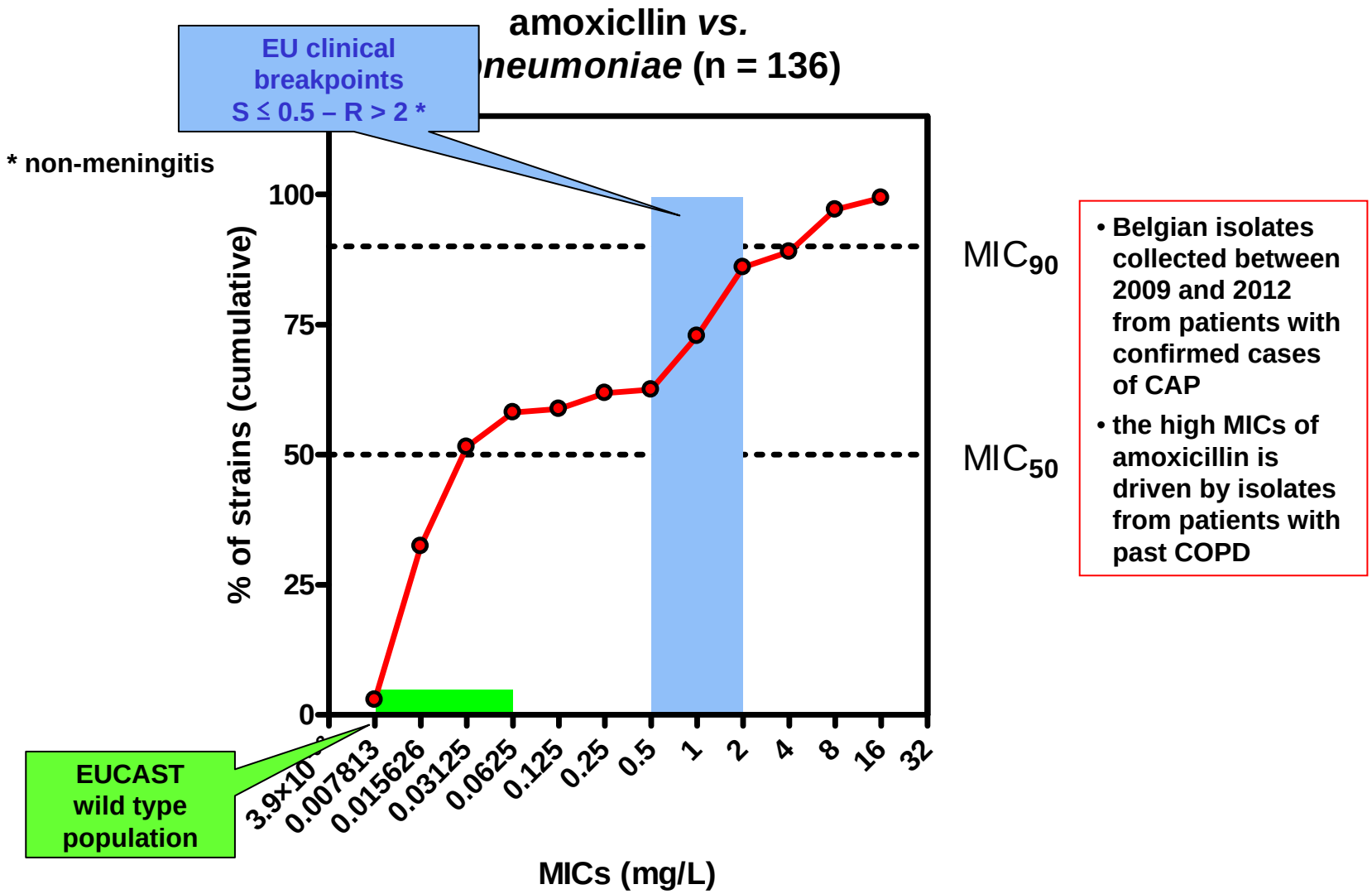


- **Belgian isolates collected between 2009 and 2012 from patients with confirmed cases of CAP**
- **the high MICs of amoxicillin is driven by isolates from patients with past COPD**

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

MIC distribution is a continuous variable…

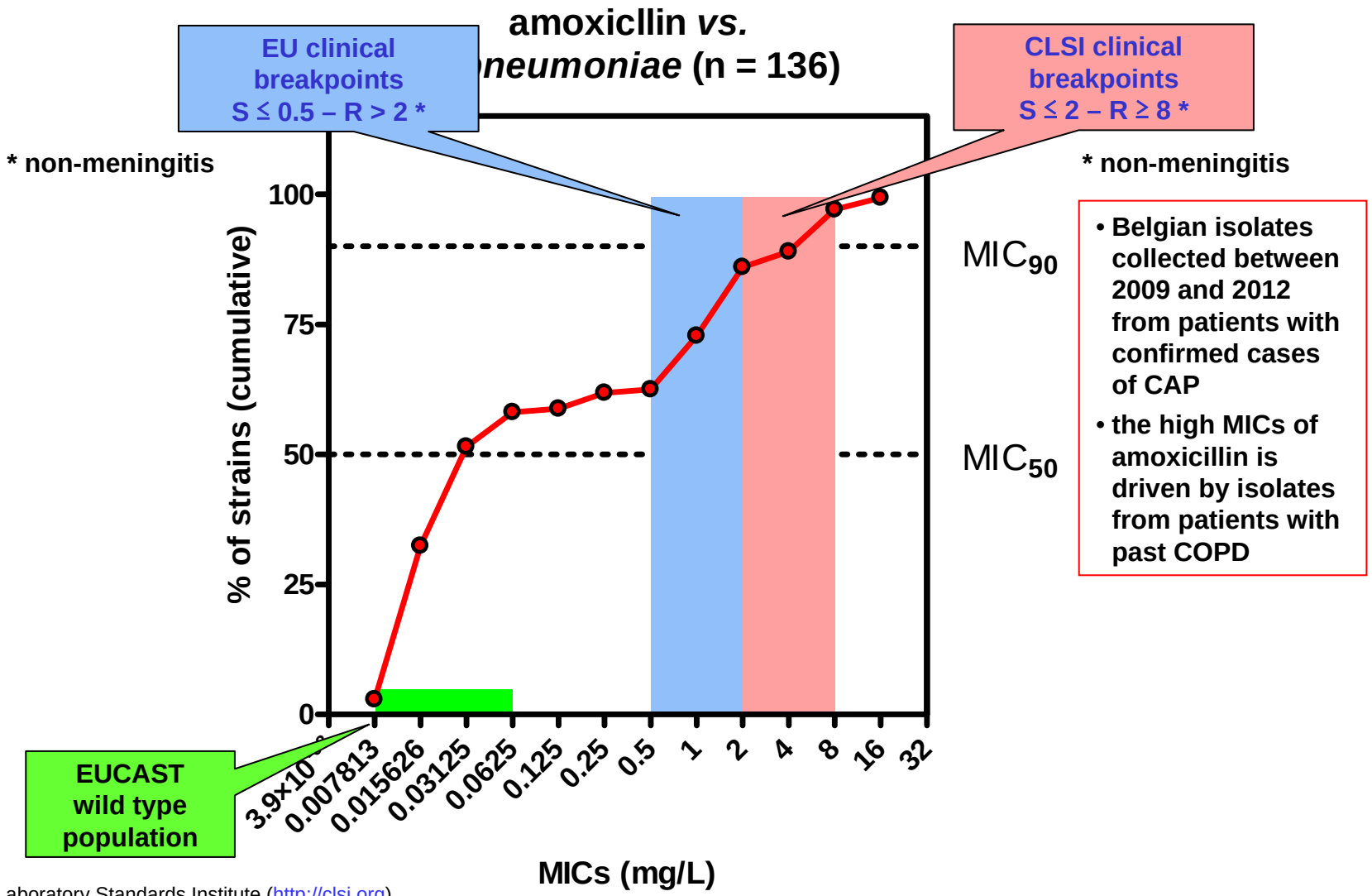


- **Belgian isolates collected between 2009 and 2012 from patients with confirmed cases of CAP**
- **the high MICs of amoxicillin is driven by isolates from patients with past COPD**

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

Tulkens, unpublished

MIC distribution is a continuous variable…

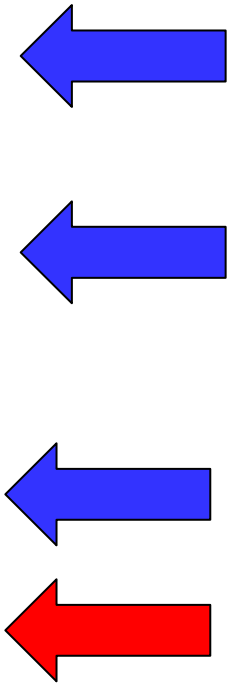


CLSI: Clinical and Laboratory Standards Institute (http://clsi.org)
EUCAST: European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org)
MIC: minimum inhibitory concentration
CAP: community-acquired pneumonia
COPD: chronic obstructive pulmonary disease

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)

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

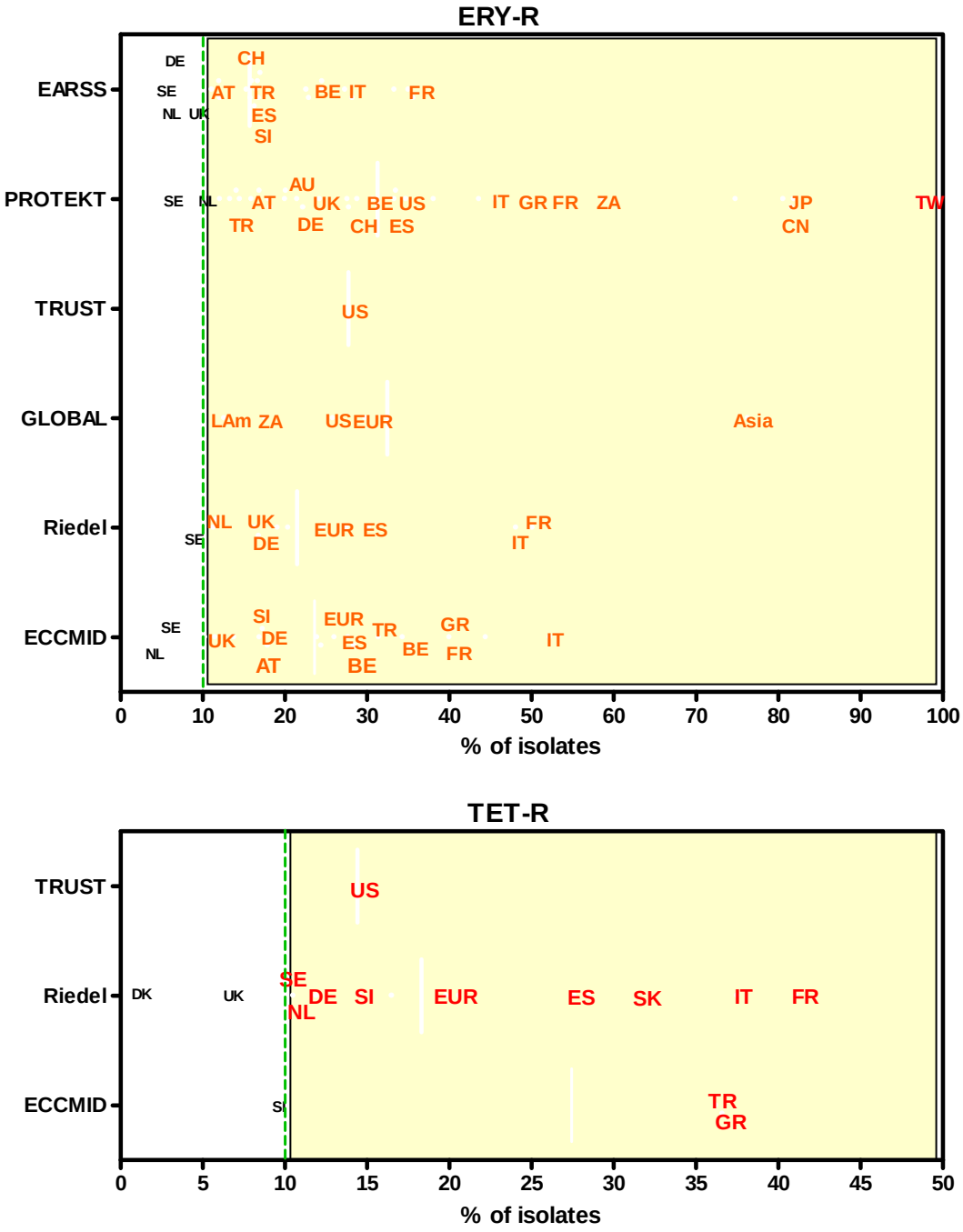
*analysis of resistance to erythromycin and doxycycline (with CAP as main indication) in surveillance systems or publications (*S. pneumoniae*)

- **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



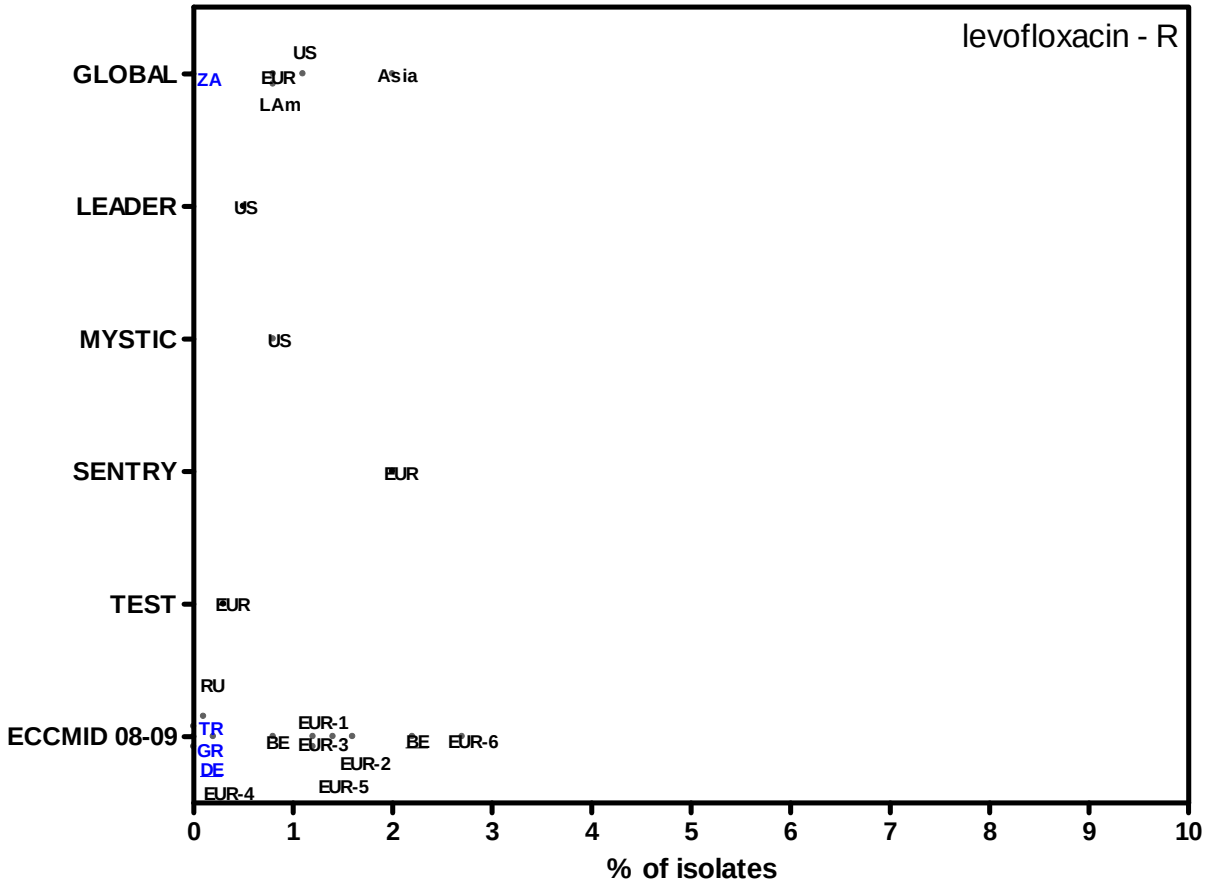
Resistance of *S. pneumoniae* to fluroquinolones

*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

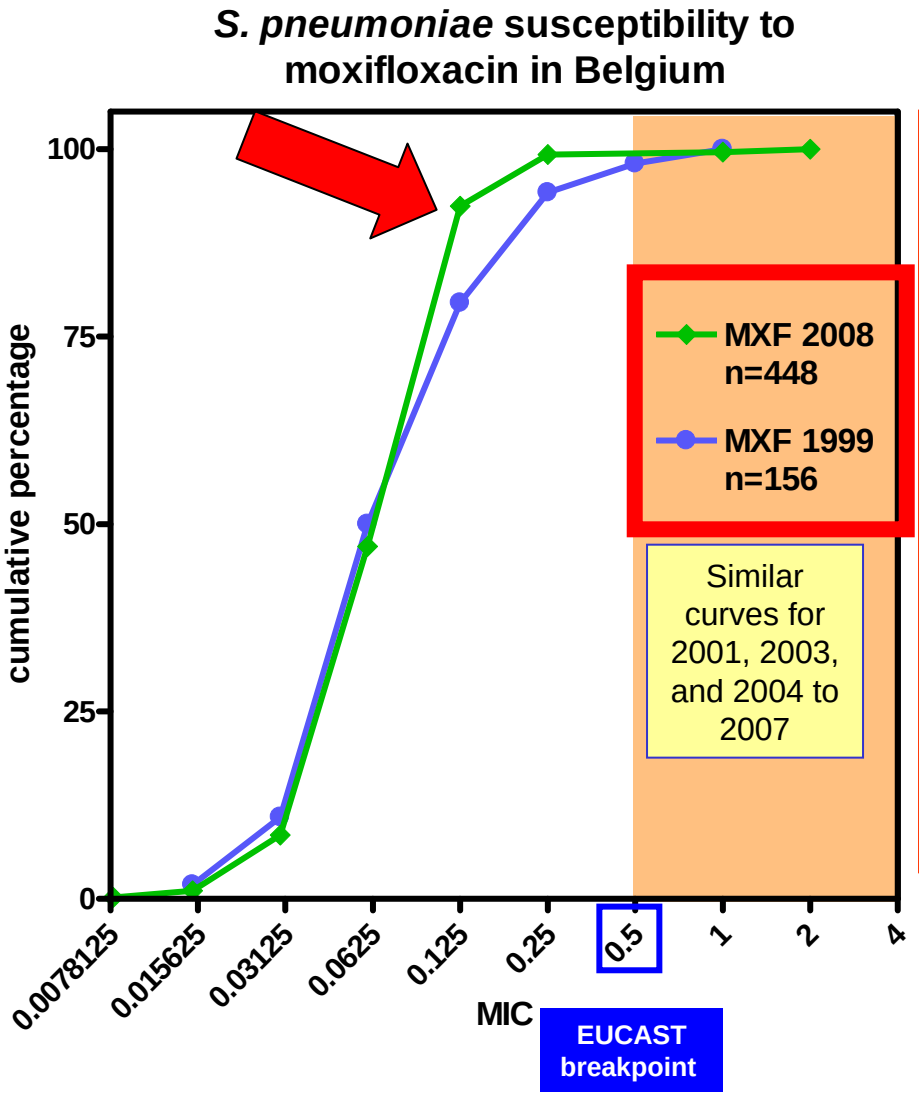
- levofloxacin: S ≤2 – R ≥8
- doxycycline: S ≤1 – R ≥4



Lismond *et al.*, in preparation

CAP: community-acquired pneumonia

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



- Extract from the data of a national collection based on annual surveys made by the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates [https://www.wiv-isp.be/Programs/communicable-infectious-diseases/Pages/EN-BacterialDiseases.aspx?pflg=1033] and presented at the 19th ECCMID. May, 16-19 2009, Helsinki (Vanhoof *et al* abstract no. O467 [http://www.blackwellpublishing.com/eccmid19/abstract.asp?id=74082; last visited: 2 may 2014])
- See also
  - Vanhoof *et al* Acta Clin Belg. 2006;61:49-57
  - Vanhoof *et al* Pathol Biol (Paris) 2010;58:147-151)
- Confirmed in an independent study for the period 2004-2009 (Simoens *et al* Antimicrob Agents Chemother 2011;55:3051-3)
- Similar distribution for blood-stream isolates from patients with clinically confirmed diagnostic of CAP in 2007-2010 (Lismond *et al* Int J Antimicrob Agents. 2012;39(3):208-216)

MXF: moxifloxacin
CAP: community-acquired pneumoni
MIC: minimum inhibitory concentration

Resistance of *S. pneumoniae* to fluroquinolones

- 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 fluroquinolones

- 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 Contries (all cases from Korea, Hong-Kong, Taiwan) in a
    fluoroquinolo
    associated i

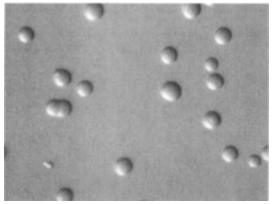
Table 2 Independent risk factors associated with pneumonia caused by levofloxacin-nonsusceptible *S. pneumoniae*

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

Mycoplasma pneumoniae



Waites & Talkington, Clin. Microbiol. Rev. 2004;17:697-728

- must be recognized as a real potential pathogen if performing active surveillance

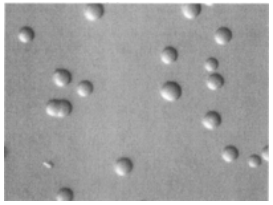
CLINICAL MICROBIOLOGY REVIEWS, Oct. 2004, p. 697–728
0893-8512/04/$08.00+0 DOI: 10.1128/CMR.17.4.697–728.2004 Vol. 17, No. 4

Mycoplasma pneumoniae and Its Role as a Human Pathogen

Ken B. Waites[1]* and Deborah F. Talkington[2]

Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama 35249,[1] and Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333[2]

Mycoplasma pneumoniae



Waites & Talkington, Clin. Microbiol. Rev. 2004;17:697-728

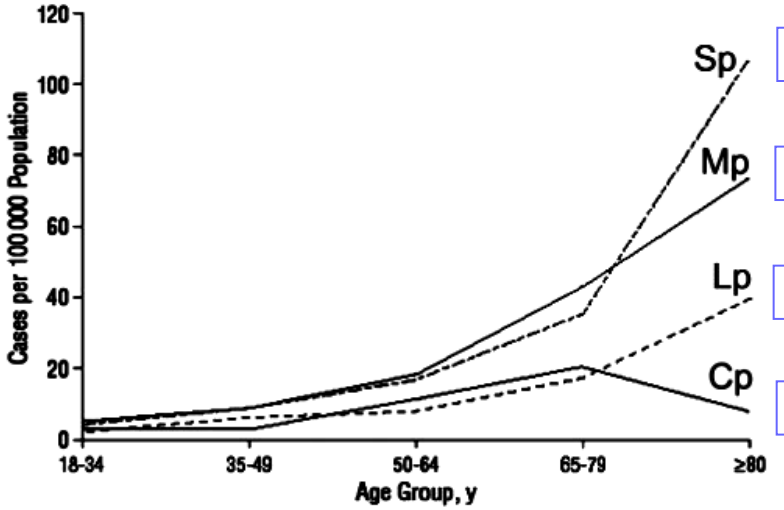
- must be recognized as a real potential pathogen if performing active surveillance

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2004, p. 697–728
0893-8512/04/$08.00+0 DOI: 10.1128/CMR.17.4.697–728.2004 Vol. 17, No. 4

Mycoplasma pneumoniae and Its Role as a Human Pathogen

Ken B. Waites[1]* and Deborah F. Talkington[2]

Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama 35249,[1] and Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333[2]



S. pneumoniae

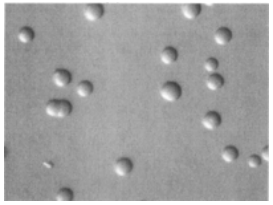
M. pneumoniae

L. pneumophila

C. pneumonaie

FIG. 6. Data from an active surveillance study performed in Ohio in 1991, showing age-specific rates of community-acquired pneumonia due to the major bacterial pathogens. *M. pneumoniae* infections were diagnosed by seroconversion, using CF tests. These data demonstrate that *M. pneumoniae* causes a relatively large proportion of pneumonias of sufficient severity to warrant hospitalization among persons younger than 50 years but that it is also an important cause of pneumonia in older age groups. Sp, *S. pneumoniae*; Mp, *M. pneumoniae*; Lp, *L. pneumophila*; Cp, *C. pneumoniae*. Reprinted from reference 283 with permission of the publisher.

Mycoplasma pneumoniae



Waites & Talkington, Clin. Microbiol. Rev. 2004;17:697-728

- was long considered as universally susceptible to macrolides…
- but this was no longer true in Asia since several years …

AAC Journals.ASM.org

Antimicrob Agents Chemother. 2013;57:4046-9.

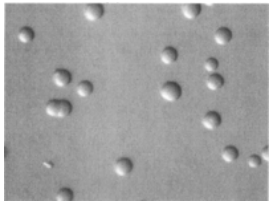
Nationwide Surveillance of Macrolide-Resistant *Mycoplasma pneumoniae* Infection in Pediatric Patients

Yasuhiro Kawai,[a] Naoyuki Miyashita,[b] Mika Kubo,[a] Hiroto Akaike,[a] Atsushi Kato,[a] Yoko Nishizawa,[a] Aki Saito,[a] Eisuke Kondo,[a] Hideto Teranishi,[a] Tokio Wakabayashi,[a] Satoko Ogita,[a] Takaaki Tanaka,[a] Kozo Kawasaki,[a] Takashi Nakano,[a] Kihei Terada,[a] Kazunobu Ouchi[a]

Department of Pediatrics[a] and Department of Internal Medicine 1,[b] Kawasaki Medical School, Okayama, Japan

We conducted nationwide surveillance to investigate regional differences in macrolide-resistant (MR) *Mycoplasma pneumoniae* strains in Japan. The prevalence of MR *M. pneumoniae* in pediatric patients gradually increased between 2008 and 2012. Although regional differences were observed, high levels of MR genes were detected in all seven surveillance areas throughout Japan and ranged in prevalence from 50% to 93%. These regional differences were closely related to the previous administration of macrolides.

Mycoplasma pneumoniae



Waites & Talkington, Clin. Microbiol. Rev. 2004;17:697-728

- was long considered as universally susceptible to macrolides…
- but this was no lo

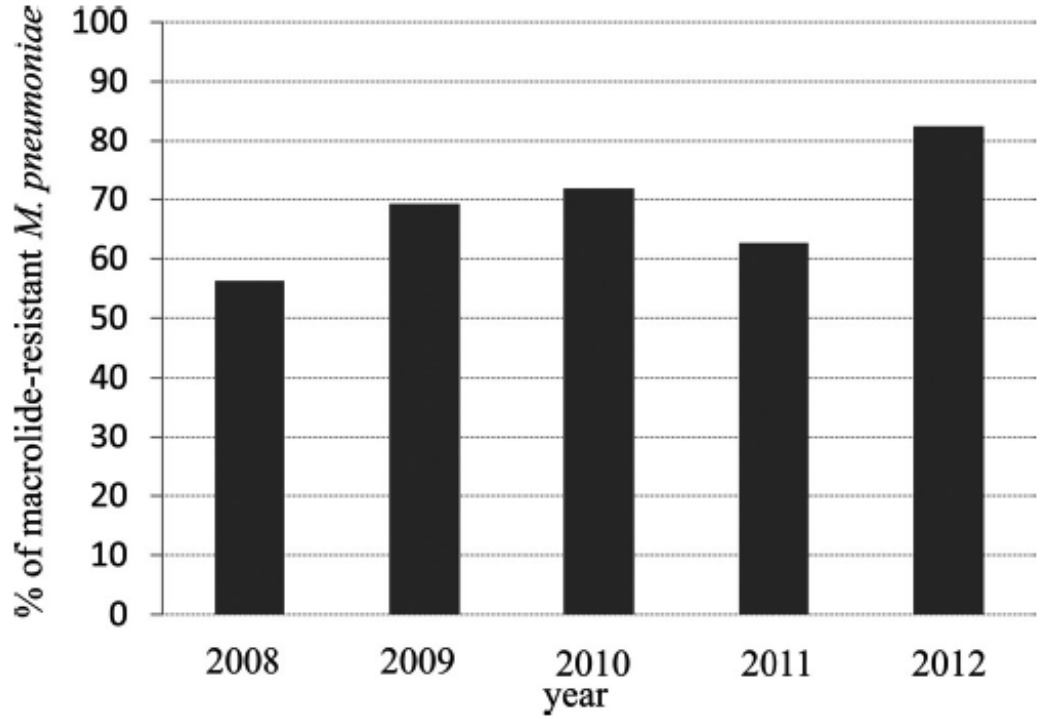
AAC Journals.ASM.org **Antimicrob Agents Chemot**

Nationwide Surveillance of Macrolide-R
pneumoniae Infection in Pediatric Patie

Yasuhiro Kawai,[a] Naoyuki Miyashita,[b] Mika Kubo,[a] Hiroto Akaike,[a] Atsushi
Hideto Teranishi,[a] Tokio Wakabayashi,[a] Satoko Ogita,[a] Takaaki Tanaka,[a] Ko
Kazunobu Ouchi[a]

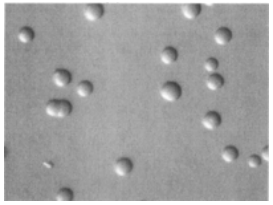
Department of Pediatrics[a] and Department of Internal Medicine 1,[b] Kawasaki Medical School, O

We conducted nationwide surveillance to investigate regional differences in
strains in Japan. The prevalence of MR *M. pneumoniae* in pediatric patients
gional differences were observed, high levels of MR genes were detected in al
prevalence from 50% to 93%. These regional differences were closely related



l Year-by-year increases in the frequency of macrolide-resistant *Mycoplasma pneumoniae* cases from 2008 to 2012.

Mycoplasma pneumoniae



Waites & Talkington, Clin. Microbiol. Rev. 2004;17:697-728

- and Resistance is arriving in Europe

AAC Journals.ASM.org

Antimicrobial Agents and Chemotherapy 2014 58 1265–1266

LETTER TO THE EDITOR

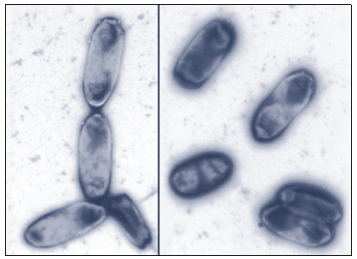
First Report of Macrolide Resistance in a *Mycoplasma pneumoniae* Isolate Causing Community-Acquired Pneumonia in Spain

Juan de Dios Caballero,[a,b,c] Rosa del Campo,[a,b,c] María del Carmen Mafé,[d] María Gálvez,[a] Mario Rodríguez-Domínguez,[a,b,c] Rafael Cantón,[a,b,c] María Antonia Meseguer,[a] José Manuel Hermida[d]

Servicio de Microbiología, Hospital Universitario Ramón y Cajal, Madrid, Spain[a]; Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain[b]; Spanish Network for Research in Infectious Diseases (REIPI), Instituto de Salud Carlos III, Madrid, Spain[c]; Servicio de Enfermedades Infecciosas, Hospital Universitario Ramón y Cajal, Madrid, Spain[d]

A previously healthy 23-year-old Chinese who had been studying in Spain for 1 year but returned from a 1-month trip to China and Korea 13 days before the onset of symptoms.

Haemophilus: is it important ?



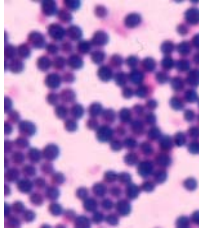
http://www.pathologyoutlines.com/topic/lymphnodeshinfluenzae.html

- *Haemophilus* is often considered as a colonizer of the upper respiratory tract with risks only for patients with COPD
- However, in coinfection with a preceding viral infection, *Haemophilus* may easily colonize the lung, leading to lethal secondary bacterial pneumonia.
  - We may now understand the corresponding genetic background (e.g. overexpression of an anti-oxidant protein) [1]
- β-lactamase-negative ampicillin-resistant (BLNAR) *Haemophilus* may be on the rise in some regions in Europe (but not all) [2]
  - antibiotic discs may fail to fully separate between BLNAS and BLNAR populations [3]
  - the majority of invasive *H. influenzae* (including BLNAR) remain susceptible to third-generation cephalosporins and fluroquinolones in Europe [4]
- Resistance of Haemphilus to fluroquinolones may be on the rise in Asia [5]

COPD chronic obstructive pulmonary disease
BLNAR β-lactamase-negative ampicillin-resistant
BLNAS β-lactamase-negative ampicillin-sensitive

1. Wong, *et al. Proc Natl Acad Sci U S A*. 2013;110:15413-8.
2. Dabernat, *et al. Eur J Clin Microbiol Infect Dis*. 2012;31:2745-53
   Geelen, *et al.* Scand J Infect Dis. 2013;45:606-11
3. Garcia-Cobos, *et al. JAC*. 2013;68: 159–63
4. Garcia-Cobos, *et al JAC*. 2014;69:111-6
   Puig, *et al.. PLoS One*. 2013;13-8:e82515
5. Shoji, *et al. J Infect Chemother*. 2014;20:250-5

Staphylococcus aureus



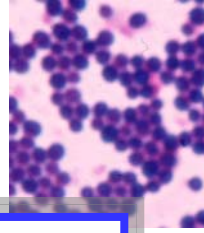
http://www.microbeworld.org/index.php?option=com_jlibrary&view=article&id=7611

- Nosocomial pneumonia involving hospital-acquired (HA) *S. aureus* is becoming increasingly frequent [1,2]
- In parallel, pneumonia caused by community-acquired (CA) MRSA while remaining rare in Europe[2] are becoming common in several other parts of the world including Asia [3]
- As many strains (even MSSA) produce toxins, they cause major tissue damage, and, hence a high mortality [3,4,5]

1. Jones, *Clin Infect Dis.* 2010;51(suppl 1):S81-7
2. Valour, *et al Rev Pneumol Clin*. 2013;69:368-82
3. Karampela, *et al. Minerva Anestesiol*. 2012 Aug;78(8):930-40
   Kang & Song. *Infect Chemother.* 2013;45:22-31
4. Papazian & Donati. Nosocomial pneumonia. *In* Infectious Diseases, 3rd Edition, Cohen, Powderly & Opal, eds. Elsevier
   (available on line at http://www.expertconsultbook.com ; last visisted: 4 April 2014)
5. Catena, *et al Infez Med*. 2012;20:205-10 /.

MRSA methicillin-resistant *Staphylococcus aureus*
MSSA methicillin-sensitive *Staphylococcus* aureus

S. aureus



- Nosocomial pneum
  S. aureus is becom
- In parallel, pneumo
- A
  major tissue dama

"***S. aureus* accounts for 2 to 5% of the etiologies of community-acquired pneumonia"**

"***S. aureus* represents 20 to 30% of cases of hospital-acquired pneumonia, including ventilator-associated pneumonia"**

1. Jones Cli S81-7
2.

Revue de Pneumologie clinique (2013) xxx, xxx–xxx

ELSEVIER MASSON

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

SÉRIE : MICROBIOLOGIE ET APPAREIL RESPIRATOIRE

Infections broncho-pulmonaires à *Staphylococcus aureus*

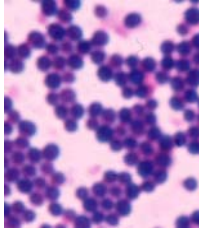
Staphylococcus aureus broncho-pulmonary infections

F. Valour[a,b,c,d], N. Chebib[a], Y. Gillet[b,c,d,e], P. Reix[b,f], F. Laurent[b,c,d,g], C. Chidiac[a,b,c,d], T. Ferry[a,*,b,c,d]

[a] *Service des maladies infectieuses et tropicales, hospices civils de Lyon, hôpital de la Croix-Rousse, groupement hospitalier Nord, 103, Grande-Rue-de-la-Croix-Rousse, 69004 Lyon, France*
[b] *Université Claude-Bernard Lyon 1, 69008 Lyon, France*
[c] *Inserm U1111, CNRS UMR5308, ENS de lyon, UCBL1, Centre international de recherche en infectiologie (CIRI), 69007 Lyon, France*
[d] *Centre national de référence des staphylocoques, hospices civils de Lyon, 69008 Lyon, France*
[e] *Service d'urgences pédiatriques, hospices civils de Lyon, hôpital Femme–Mère-Enfant, 69500 Bron, France*
[f] *Service de pneumologie, allergologie, mucoviscidose, hospices civils de Lyon, hôpital Femme–Mère-Enfant, 69500 Bron, France*
[g] *Laboratoire de bactériologie, hospices civils de Lyon, groupement hospitalier Nord, 69004 Lyon, France*

Valour, *et al Rev Pneumol Clin*. 2013;69:368-82

S. aureus



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

- Nosocomial pneumonia involving hospital-acquired (HA) *S. aureus*
- In parallel (CA) MRS in several
- As many s major tissu

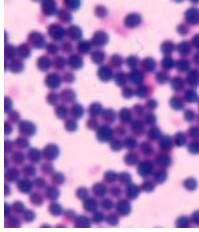
1. Jones Clin Infect Dis 2
2. Karampela et al Minerv
3. Papazian & Donati Nos http://www.expertconsu

Table 3. Regional Incidence of Pathogens Isolated from Patients Hospitalized with Pneumonia in the Last 5 Years of the SENTRY Antimicrobial Surveillance Program (31,436 Cases).

	Incidence, %			
Pathogen	All regions	United States	Europe	Latin America
Staphylococcus aureus	28.0	36.3	23.0	20.1
Pseudomonas aeruginosa	21.8	19.7	20.8	28.2
Klebsiella species	9.8	8.5	10.1	12.1
Escherichia coli	6.9	4.6	10.1	5.5
Acinetobacter species	6.8	4.8	5.6	13.3
Enterobacter species	6.3	6.5	6.2	6.2
Serratia species	3.5	4.1	3.2	2.4
Stenotrophomonas maltophilia	3.1	3.3	3.2	2.3
Streptococcus pneumoniae	2.9	2.5	3.6	2.4
Haemophilus influenzae	2.7	2.5	3.7	1.3

Jones Clin Infect Dis 2010;51(suppl 1):S81-7

S. aureus



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

- Nosocomial pne… HA)
  S. aureus is be…
- In parallel, pneu… ed
  (CA) MRSA wh… mon
  in several other…
- As many strains… ause
  major tissue da…

Table 4. Frequency of Bacterial Pathogens Associated with Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP)

Organism	Percentage of isolates (no) HABP (n = 835)	VABP (n = 499)
MRSA	47.1 (48.6)	42.5 **(34.4)**
Pseudomonas species	18.4	21.2
Klebsiella species	7.1	8.4
Haemophilus species	5.6	**12.2**
Enterobacter species	4.3	5.6
Streptococcus pneumonaie	3.1	5.8
Acinetobacter species	2.0	3.0

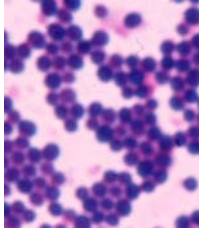
NOTE. Data are from [2, 7]. Boldface indicates a significant change or difference in incidence compared with HABP. MRSA, methicillin-resistant *Staphylococcus aureus*.

1. Jones Clin Infect Dis 2010;51(suppl 1…
2. Karampela et al Minerva Anestesiol. …
3. Papazian & Donati Nosocomial pneu… at
   http://www.expertconsultbook.com (L… 2013;69:368-82.

HABP: hospital-acquired bacterial pneumonia
VABP: ventilator-associated bacterial pneumonia
MRSA: methicillin resistant *Staphylococcus aureus*

Jones, *et al. Clin Infect Dis*. 2010;51(suppl 1):S81-7

S. aureus



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

- Nosocom
  S. aureus
- In paralle
  (CA) MRS
  in several
- As many
  major tiss

1. Jones Clin Infect Dis
2. Karampela et al Mine
3. Papazian & Donati N
   http://www.expertcons

Le Infezioni in Medicina, n. 3, 205-210, 2012

Casi clinici

Case reports

Necrotizing pneumonia caused by Panton-Valentine leukocidin-producing methicillin-susceptible *Staphylococcus aureus* (MSSA)

Polmonite necrotizzante causata da Staphylococcus aureus *meticillino sensibile produttore di leucocidina di Panton-Valentine (MSSA)*

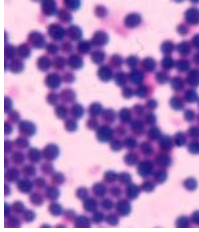
Vincenzo Catena[1,2], Marco Baiocchi[2], Paolo Lentini[3], Luigi Badolati[2], Monica Baccarin[2], Daniele D. Del Monte[1], Alessandro Rubini[4]

[1]Dipartimento di Emergenza e Terapia Intensiva, U.L.S.S. 2, Feltre, Belluno, Italy;
[2]Dipartimento di Emergenza e Terapia Intensiva, Ospedale "San Bassiano", Bassano del Grappa, Vicenza, Italy;
[3]Dipartimento Nefrologia e Dialisi, Ospedale "S. Bassiano", Bassano del Grappa, Vicenza, Italy;
[4]Dipartimento Scienze Biomediche, Università di Padova, Padova, Italy

8-82.

Catena, *et al Infez Med*. 2012;20:205-10

S. aureus



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

- Nosocomial pne… …HA)
  S. aureus is bec…
- In parallel, pneu… …d
  (CA) MRSA whi… …on
  in several other …
- As many strains… …ause
  major tissue dar… …3]

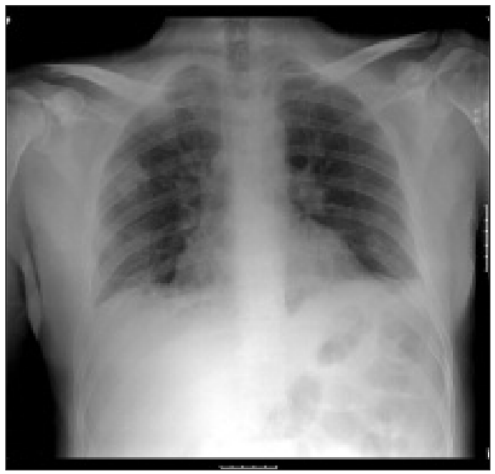


Figure 1 - Chest X-Ray at the admission.

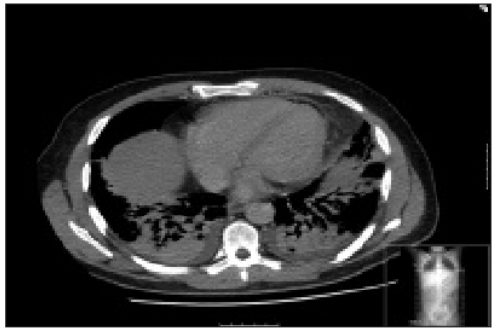
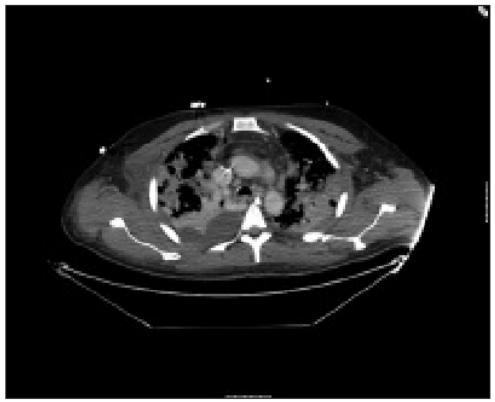


Figure 2 - Chest CT scan at the admission: diffuse bilateral alveolar infiltrates.



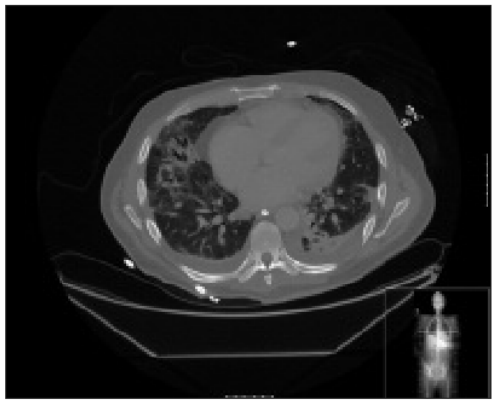


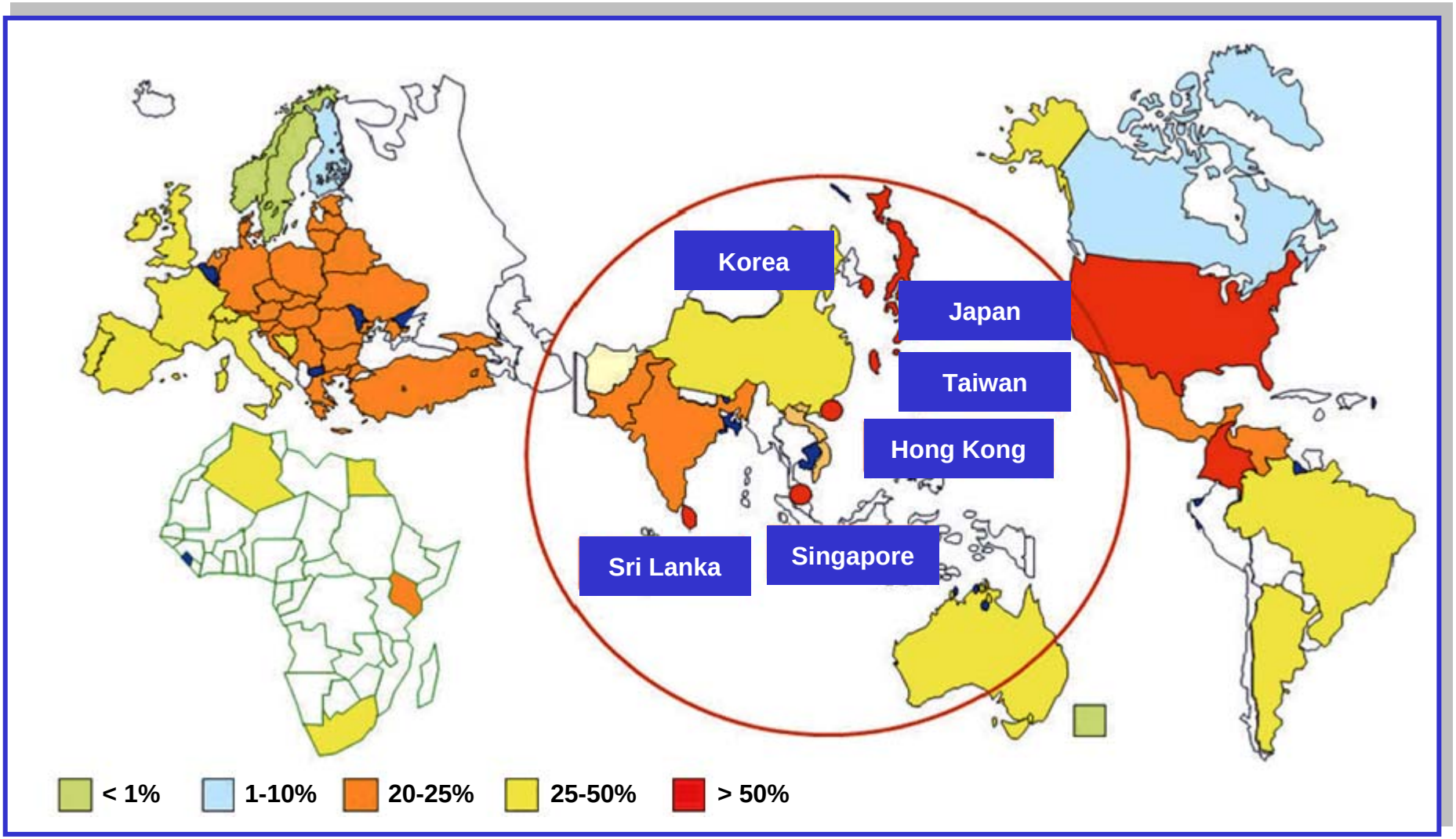
Figure 3 - Chest CT scans during ICU stay: extensive bilateral pleural effusions diffuse bilateral alveolar infiltrates and nodular opacities with cavity forming consistent with necrotizing pneumonia.

Catena, *et al.* Infez Med. 2012;20:205-10

1. Jones Clin Infect Dis 2010;51(suppl 1)…
2. Karampela et al Minerva Anestesiol. 2…
3. Papazian & Donati Nosocomial pneum… …013;69:368-82.
   http://www.expertconsultbook.com (La…

MRSA in Asia

Prevalence of methicillin resistance among *S. aureus* isolates.
Some Asian countries have shown the highest prevalence rates of MRSA



MRSA **methicillin restistant *Staphylococcus aureus***

Kang & Song. *Infect Chemother* 2013;45:22-31

S. aureus in Africa

- Very little is known about Africa !
- But data that are coming are challenging…

Huson *et al.* Infection. 2014 Jan 25. [Epub ahead of print]

- high prevalence (20-28 %) of MRSA in urban hopitals (as opposed to rural) in Cameroon
- typical case of *S. aureus* pneumonia (strain resistant to penicillin, cloxacillin, ciprofloxacin, and erythromycin)

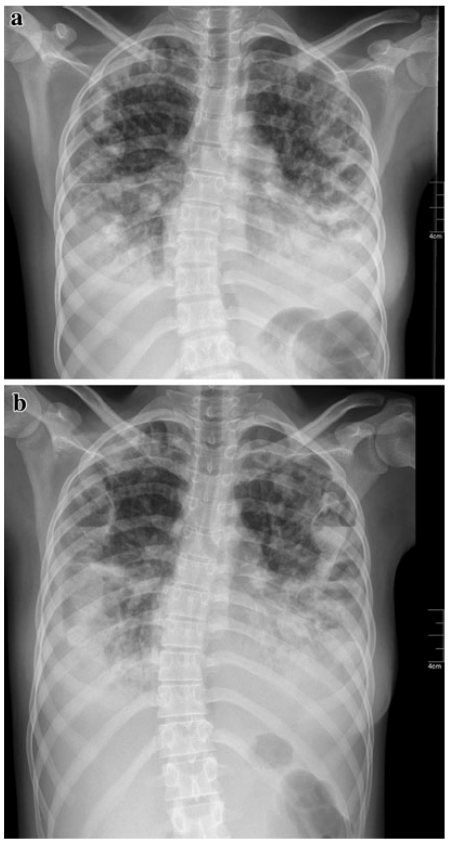
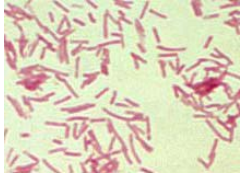


Fig. 1 **a** Chest X-ray at admission shows bilateral infiltrates and cavitary lesions. **b** Chest X-ray 6 days after admission demonstrates deterioration of cavitary lesions with air–fluid levels

MRSA: methicillin resistant *Staphylococcus aureus*

Anaerobes and lung diseases



B. fragilis
CDC Public Health
Image Library
http://phil.cdc.gov/phil

- Anaerobic bacteria are frequent in aspiration pneumonia and associated complications (aspiration pneumonitis, lung abscess, necrotizing pneumonia and empyema) [1]
- While microbiological documentation is difficult, failure to direct adequate therapy against anaerobes (if present) may lead to clinical failures [2]
- Treatment of anaerobic infection is complicated by the slow growth of these organisms, by the polymicrobial nature of the infections, and by the growing resistance of anaerobic bacteria to antimicrobials (see next slide but only very rare cases for metronidazole [3])

1. Bartlett. *Anaerobe.* 2012;18:235-9
2. Brook. *Adv Exp Med Biol.* 2011;697:117-52 - *In* N. Curtis et al. (eds.), *Hot Topics in Infection and Immunity in Children VII*, Springer.
3. Centers for Disease Control and Prevention (CDC) MMWR *Morb Mortal Wkly Rep*. 2013;62:694-6.

Anaerobes: resistance to other antibiotics than metronidazole

EUCAST

CLSI breakpoints

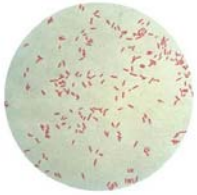
Percent resistance of *Bacteroides fragilis* group isolates to antimicrobial agents[a,b]

EUCAST	Antimicrobial	MIC breakpoint (μg/ml) Susceptible	MIC breakpoint (μg/ml) Resistant	% resistance to antimicrobial *B. fragilis*	% resistance to antimicrobial *B. fragilis* group
≤4 >8	Ampicillin-sulbactam	≤8/4	≥32/16	2.8–11	
≤4 >8	Amoxicillin-clavulanate	≤4/2	≥16/8	4–37	10–20
≤8 >16	Piperacillin-tazobactam	≤32/4	≥128/4	0–5	0–8
NA	Cefoxitin	≤16	≥64	4–25	17–33
≤1 >1	Ertapenem	≤4	≥16	1.4–10	
≤2 >8	Imipenem	≤4	≥16	0.3–7	<1–1
≤2 >8	Meropenem	<4	≥16	1.2–22	
≤1 >1	Doripenem	≤4	≥16	1.3–12	
≤4 >4	Clindamycin	≤2	≥8	10–42	32–52
IE	Moxifloxacin	≤2	≥8	10–41	14–57
no correl.	Tigecycline	≤4	≥16	2–11	2–13

[a] Including intermediate-resistant strains. Metronidazole is not included since >99% of Gram-negative strains are susceptible.

Brook, *et al* *Clin Microbiol Rev*. 2013;26:526-46
see also: Goldstein & Citron *Clin Microbiol Newsl* 2011;33:1–14.

Gram-negatives
(beyond *Haemophilus*, *Legionella*, …)



P.aeruginosa
CDC Public Health
Image Library
http://phil.cdc.gov/phil

- May coexist with Gram-positive organisms…
- But remain the primary causative pathogens of nosocomial pneumonia [1]
- Main organisms include *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter species*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* [2]
- Inadequate initial therapy is unambiguously linked with increase mortality rate [3]
- Resistance rates vary very much from hospital to hospital and from ward to ward, but risk factors may be identified [1]:
  - hospitalization > 5 days, high resistance rates in the area or specific hospital,
  - immunosuppressive diseases and/or drugs, use of antibiotics in the last 90 days,
  - for health care-associated pneumonia: hospitalization for 2 days within 90 days, residence in a nursing home or extended care facility, home infusion therapy, chronic dialysis within 30 days, home wound care, or a family member with an MDR pathogen

1. Arnold *et al* Intensive Care Med. 2010;25:259-70
2. Boucher, *et al. Clin Infect Dis*. 2009;48:1-12.
3. Leibovici, *et al.* J Intern Med 1998;244:379-86
   Ibrahim, *et al. Chest*. 2000; 118:146-55
   Regui *et al* Chest. 2002;122:262-8
   Micek *et al AAC*. 2005;1306-11.

MDR multi drug resistant

Gram-negatives
(beyond *Haemophilus*, *Legionella*, …)

Resistance

- must be assessed locally *
- often anticipated to be high *
- could be influenced by previous treatments

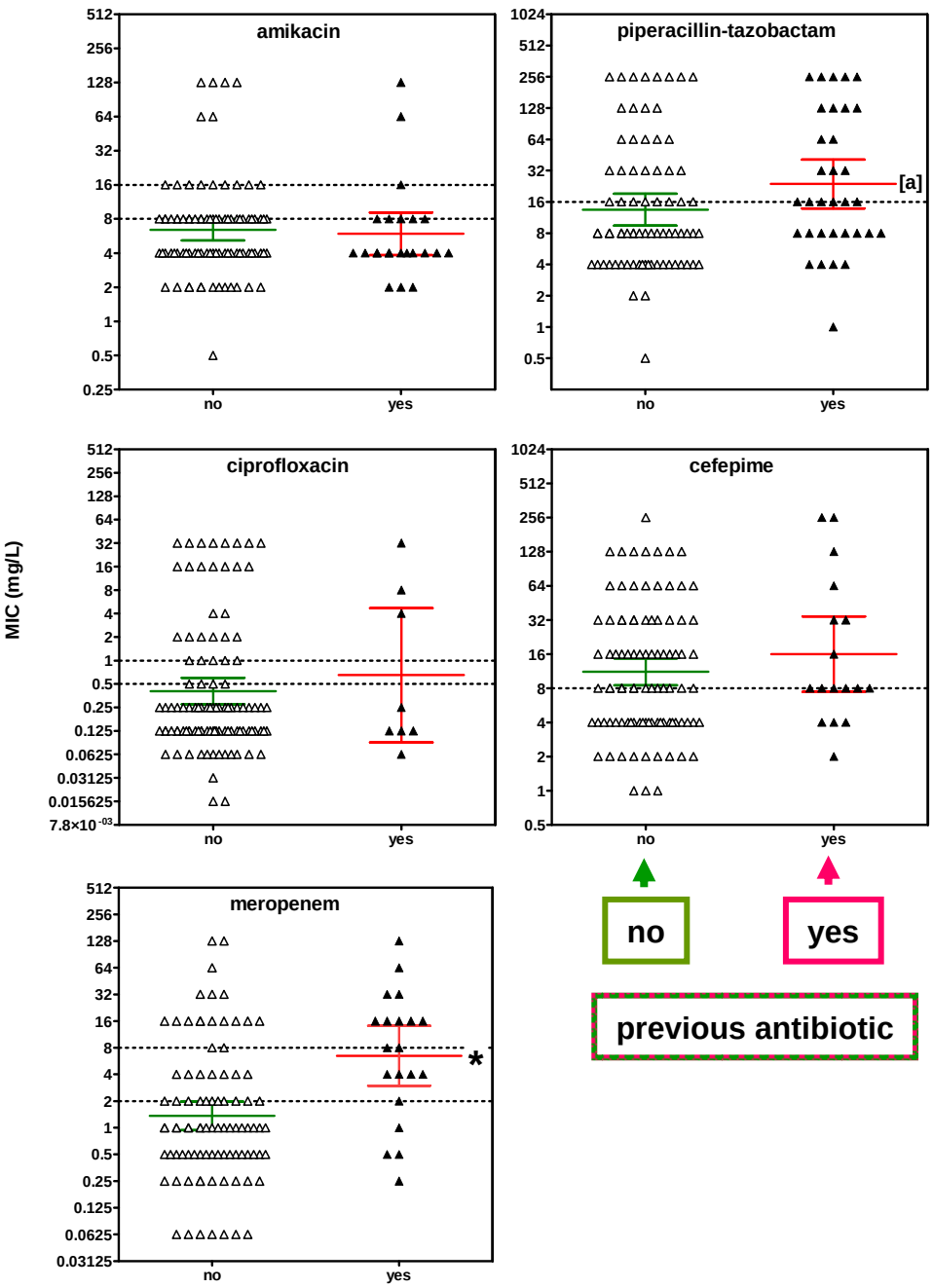
* may not be the case in all hospitals
(Sivert, *et al. Infect Control Hosp Epidemiol* 2013;34:1-14)

MIC of 5 antibiotics used in empiric antipseudomonal therapy towards initial *P. aeruginosa* isolates of ICU patients with suspected nosocomial infection in 5 hospitals in Belgium

- **stratification between patients having either not received (no) or received (yes) the corresponding drug within 1 month prior to the collection of the isolate.**
- **the horizontal dotted lines are the corresponding S and R EUCAST breakpoints**

ICU intensive care unit

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



Gram-negatives in Europe and Mediterranean Area

International Journal of Antimicrobial Agents 43 (2014) 328–334

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: Results from the SENTRY Antimicrobial Surveillance Program, 2009–2012

Helio S. Sader*, David J. Farrell, Robert K. Flamm, Ronald N. Jones

JMI Laboratories, 345 Beaver Kreek Center, Suite A, North Liberty, IA 52317, USA

Sader, *et al. Int J Antimicrob Agents*. 2014;43:328–34

Gram-negatives in Europe and Mediterranean Area

International Journal of Antimicrobial Agents 43 (2014) 328–334

Antimicrobial susceptibi
from patients hospitalise
hospitals: Results from t
Program, 2009–2012

Helio S. Sader*, David J. Farrell,
JMI Laboratories, 345 Beaver Kreek Center, Suite A, No

Antimicrobial susceptibility of Gram-negative bacterial organisms isolated from patients hospitalised with pneumonia in US and Europe and the Mediterranean region (EMR) medical centres (2009–2012).

Organism/antimicrobial agent	%S/%R (no. tested)		
	EUCAST[a]		
	USA	EMR	
Pseudomonas aeruginosa	(1439)	(1250)	
TZP	72.9/27.1	63.9/36.1	←
Ceftazidime	79.6/20.4	68.7/31.3	←
Cefepime	80.4/19.6	72.1/27.9	←
Meropenem	76.3/9.0	65.8/14.4	
Amikacin	92.2/3.8	82.8/11.2	
Gentamicin	87.0/13.0	75.2/24.8	←
Tobramycin	91.7/8.3	76.9/23.1	←
Levofloxacin	59.1/29.5	53.8/36.6	←
Colistin	98.9/1.1	99.0/1.0	

TZP: piperacillin/tazobactam

Sader, *et al. Int J Antimicrob Agents*. 2014;43:328–34

Gram-negatives in Europe and Mediterranean Area

International Journal of Antimicrobial Agents 43 (2014) 328–334

Antimicrobial susceptibi
from patients hospitalis
hospitals: Results from
Program, 2009–2012

Helio S. Sader*, David J. Farrel
JMI Laboratories, 345 Beaver Kreek Center, Suite A,

Antimicrobial susceptibility of Gram-negative bacterial organisms isolated from patients hospitalised with pneumonia in US and Europe and the Mediterranean region (EMR) medical centres (2009–2012).

Organism/antimicrobial agent	%S/%R (no. tested)	
	EUCAST[a]	
	USA	EMR
Klebsiella spp.	(666)[b]	(695)[c]
TZP	77.6/15.6	64.7/29.4
Ceftriaxone	81.4/18.2	67.6/31.7
Ceftazidime	82.0/16.4	68.9/27.9
Cefepime	83.8/13.2	71.7/24.6
Meropenem	93.1/5.9	93.1/5.0
Amikacin	90.8/8.0	89.0/5.2
Gentamicin	89.3/9.0	81.2/17.7
Levofloxacin	83.6/15.3	74.0/24.3
Tigecycline[d]	93.5/2.1	94.4/0.7
Colistin	97.3/2.7	96.4/3.6

TZP: piperacillin/tazobactam

Sader, *et al. Int J Antimicrob Agents*. 2014;43:328–34

Gram-negatives in Europe and Mediterranean Area

International Journal of Antimicrobial Agents 43 (2014) 328–334

Antimicrobial susceptibility c
from patients hospitalised wi
hospitals: Results from the SI
Program, 2009–2012

Helio S. Sader*, David J. Farrell, Robe
JMI Laboratories, 345 Beaver Kreek Center, Suite A, North Liberty

Antimicrobial susceptibility of Gram-negative bacterial organisms isolated from patients hospitalised with pneumonia in US and Europe and the Mediterranean region (EMR) medical centres (2009–2012).

Organism/antimicrobial agent	%S/%R (no. tested)	
	EUCAST[a]	
	USA	EMR
Escherichia coli	(375)	(705)
TZP	87.2/9.6	81.1/12.9
Ceftriaxone	83.7/16.0	81.8/17.7
Ceftazidime	83.2/12.5	82.3/11.9
Cefepime	85.1/11.2	83.4/13.1
Meropenem	99.5/0.0	100.0/0.0
Amikacin	97.9/0.5	95.7/1.4
Gentamicin	81.6/15.8	84.0/15.0
Levofloxacin	61.1/38.9	67.1/32.8
Tigecycline[d]	100.0/0.0	99.9/0.0
Colistin	99.7/0.3	99.9/0.1

TZP: piperacillin/tazobactam

Sader, *et al. Int J Antimicrob Agents*. 2014;43:328–34

Gram-negatives in Europe and Mediterranean Area

Inter

journa

Antimicrobial susceptibi
from patients hospitalis
hospitals: Results from
Program, 2009–2012

Helio S. Sader*, David J. Farrel

JMI Laboratories, 345 Beaver Kreek Center, Suite A,

Antimicrobial susceptibility of Gram-negative bacterial organisms isolated from patients hospitalised with pneumonia in US and Europe and the Mediterranean region (EMR) medical centres (2009–2012).

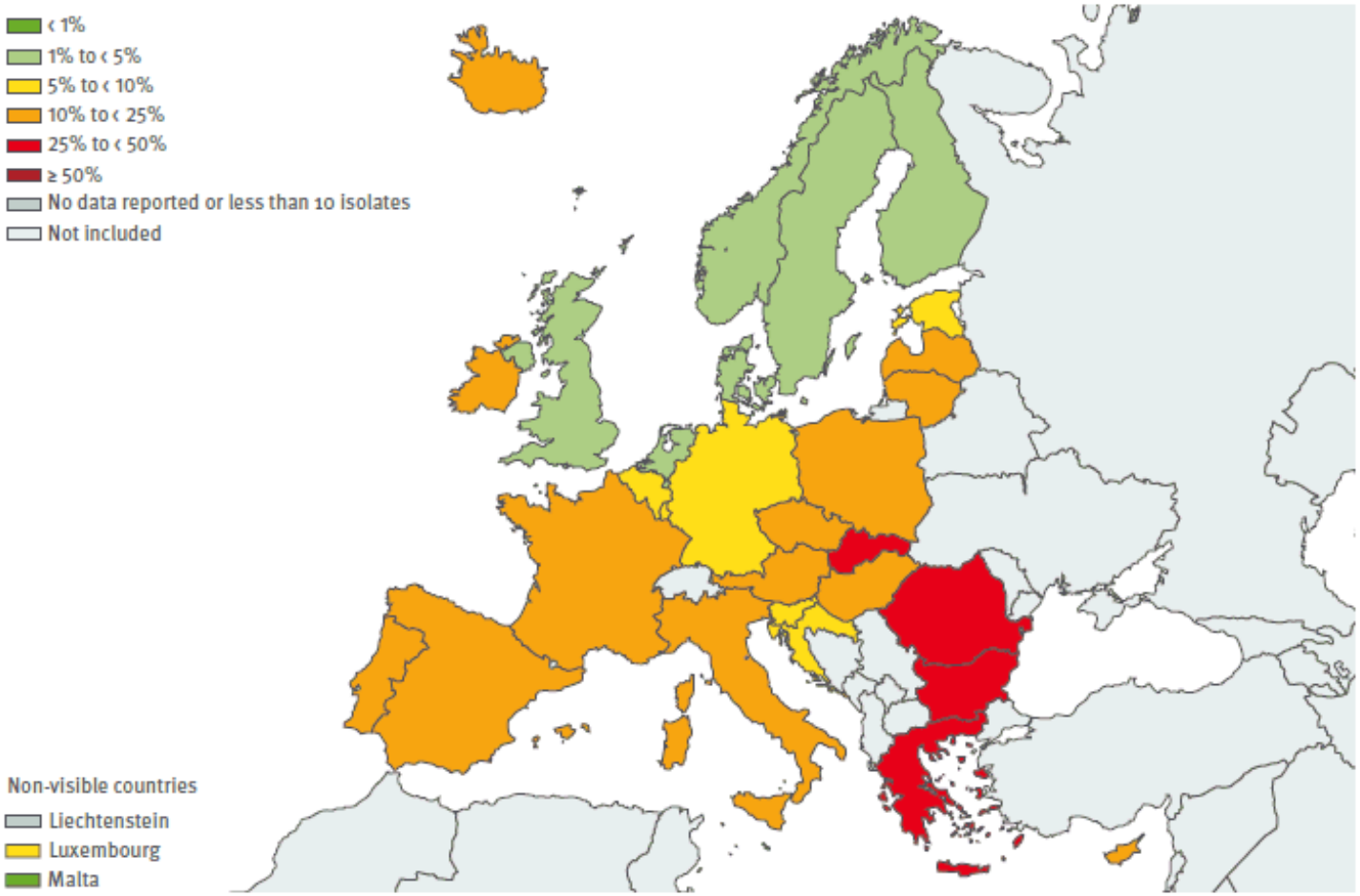
Organism/antimicrobial agent	%S/%R (no. tested)	
	EUCAST[a]	
	USA	EMR
Enterobacter spp.	(407)[f]	(330)[g]
TZP	74.0/20.6	67.0/28.2
Ceftriaxone	69.0/29.1	60.6/35.8
Ceftazidime	69.6/26.9	61.2/32.7
Cefepime	86.7/4.7	85.5/4.8
Meropenem	99.0/0.5	99.1/0.3
Amikacin	99.5/0.0	97.6/1.5
Gentamicin	94.1/5.2	92.7/6.4
Levofloxacin	93.4/4.9	89.7/8.2
Tigecycline[d]	95.6/0.7	96.4/1.2
Colistin	86.4/13.6	85.0/15.0

TZP: piperacillin/tazobactam

Sader, *et al. Int J Antimicrob Agents*. 2014;43:328–34

The problem of multiresistance: *P.aeruginosa* as an example

Figure 3.25. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with combined resistance (resistance to three or more antimicrobial classes among piperacillin (±tazobactam), ceftazidime, fluoroquinolones, aminoglycosides and carbapenems), by country, EU/EEA countries, 2012



European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2012. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2013. p.36

Emergence of resistance during treatment

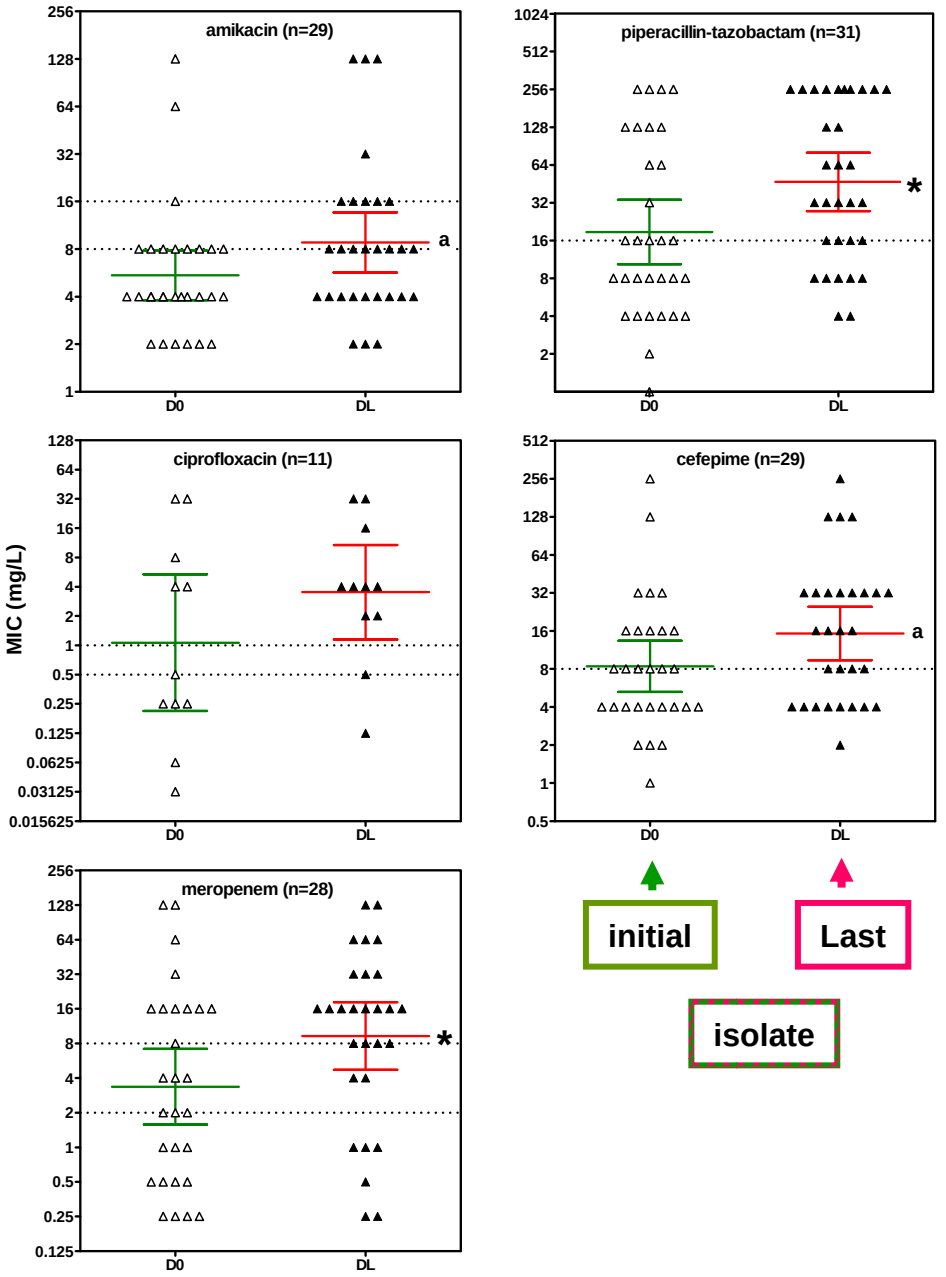
P. aeruginosa successive clonal isolates from the same patient (all patients treated with large doses of 1 to 3 antibiotics)

- 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
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**

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 ?

- **Carbapenems** ... but may be a risk factor [1] for carbapenemase and neither is better [2]
- **Ceftozolane** may help for *P. aeruginosa* (with tazobactam) [3]
- **Avibactam** may restore susceptibility to ceftazidime to a high proportion of Gram-negatives including *P. aeruginosa* [4]
- **Combining** antibiotics (based on checker board [5]) or associating of glycopeptides with colistin for ≥ 5 days [6] could help
- **Extended infusion** (of cefepime) may improve mortality, and decrease mean length of stay and hospital costs [7]
- **Continuous infusion** may be a promising approach [8] ... but may not solve the problem of emergence of resistance... (see next slide)

1. Kim, *et al. Diag Microbiol Infect Dis*. 2014;78:457–61
2. Luyt, *et al. AAC*. 2014;58:1372-80.
3. Zhanel, *et al. Drugs.* 2014;74:31–51
4. Flamm, *et al. JAC*. 2014; Advance Access
   Chalhoub et al ECCMID 2014; e-poster 440
5. Nakamura, *et al*. *J Infect Chemother.* 2014;20:266e269
6. Petrosillo, *et al. AAC*. 2014;58:851-8
7. Bauer. *et al. AAC*. 2013;57:2907-12
8. Van Herendael, *et al. Ann Intensive Care.* 2012;2:22
   Dulhunty *et al. Clin Infect Dis*. 2013;56:236-44

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

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]

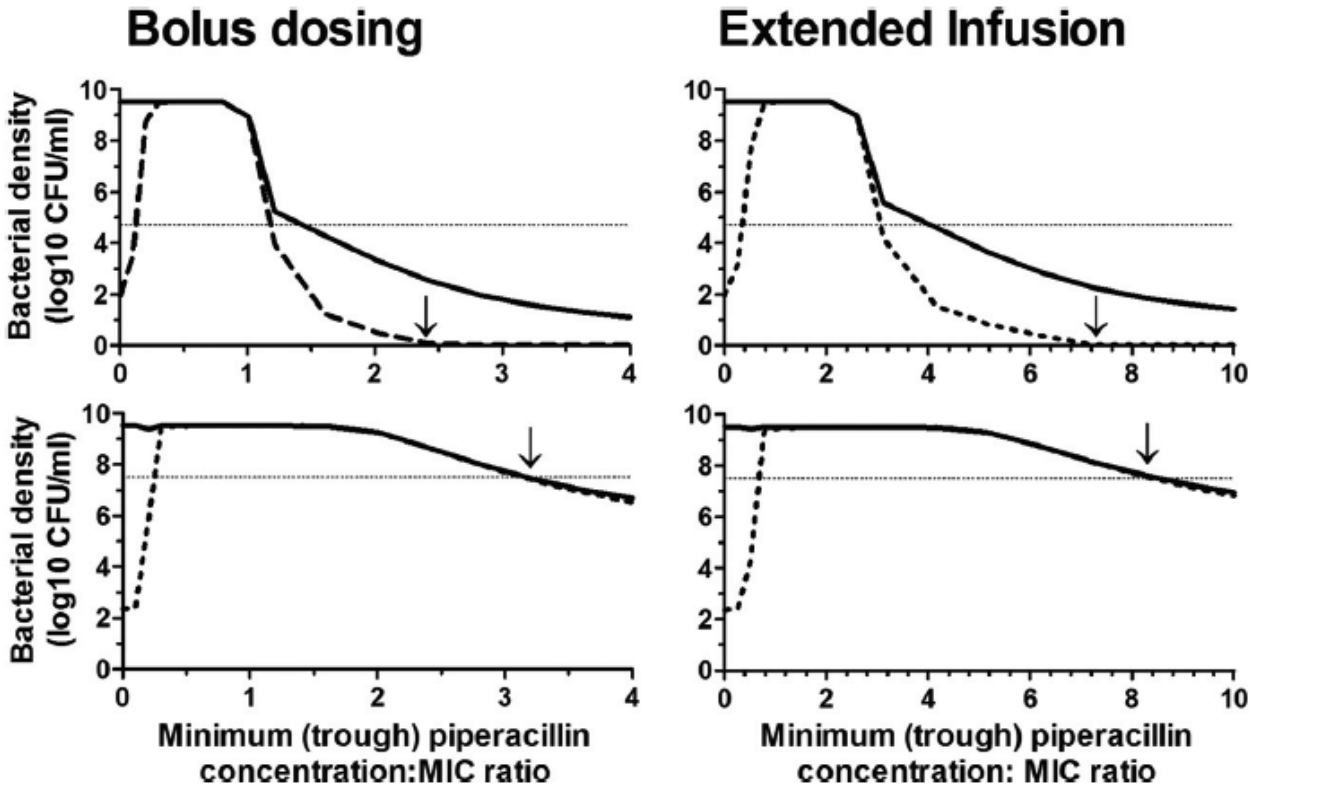


FIG 7 Change in bacterial density with the trough free piperacillin/MIC ratio following 5 days of treatment and target attainment of clinical regimens. Solid line, total population; dashed line, resistant subpopulation; dotted line, stasis line. The arrow indicates the relevant C_{min}/MIC ratio.

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

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]

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

Key questions to ask when using guidelines in infectious diseases (with application to pneumonia)

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

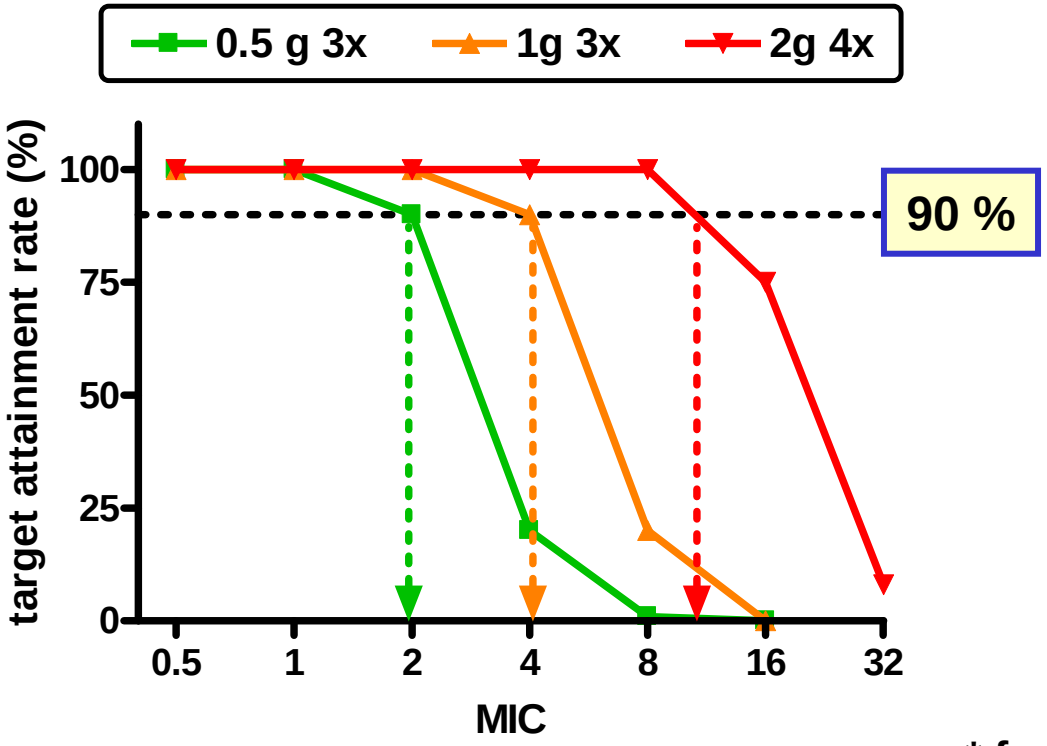
What did I not speak about ... but should have done ... since it may impact your practice

- SCVs
- persisters and biofilms
- rapid diagnostic (including resistance phenotypes and mechanisms) and moving to personalized medicine
- TDM of β-lactams and fluoroquinolones
- new drugs
- pharmacoeconomy and approaches in case of limited resources…
- ….

SCV small colony variants
TDM therapeutic drug monitorig

Back-up

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

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

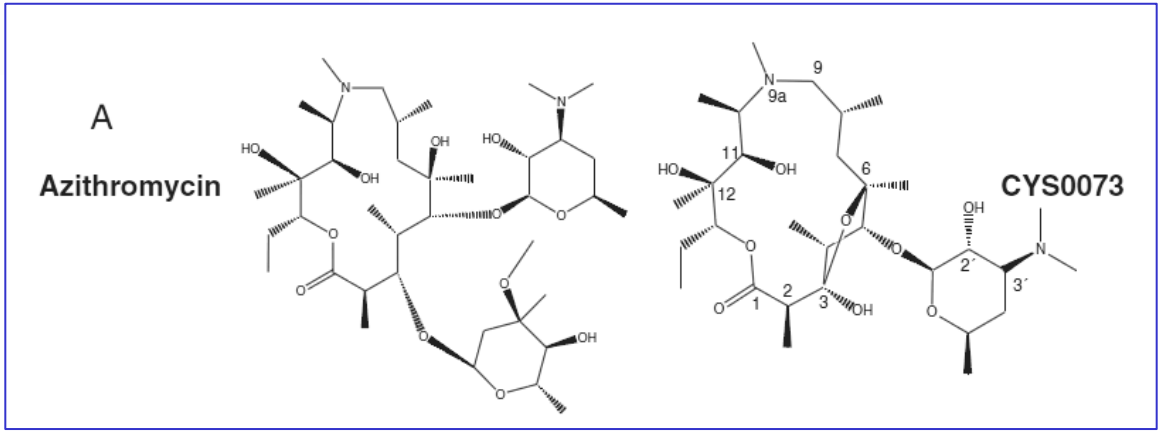
V Balloy[1,2,3,4], A Deveaux[1,2], D Lebeaux[5], O Tabary[1,2], P le Rouzic[1,2], J M Ghigo[5], P F Busson[6,7], P Y Boëlle[6,7], J Guez Guez[8], U Hahn[8], A Clement[1,2,9], M Chignard[3,4], H Corvol[1,2,9], M Burnet[8] and L Guillot[1,2]

[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

Received
5 November 2013
Revised
16 December 2013
Accepted
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
- Glo
  cur
  - –
  - –

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.
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.

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).

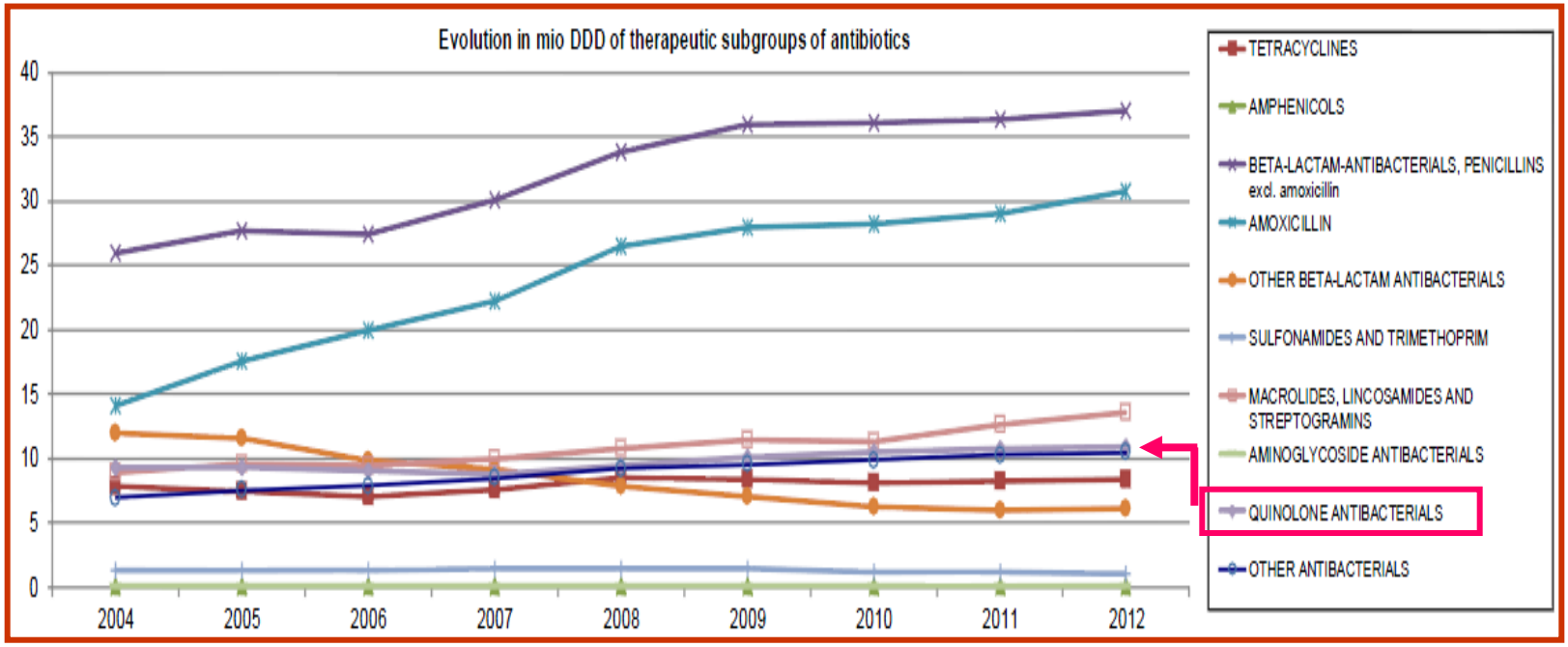
Karlowski, *et al. JAC*. 2013;68(Suppl 1): i39–i46

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

A comparison of three CAP guidelines separated by (some) water



Table 4. Recommended community-acquired pneumonia therapy and management from published international guidelines *

	BTS guidelines [24]	ATS/IDSA guidelines [25]	ERS/ESCMID guidelines [26]
Low severity patients*	Use CURB65 score with clinical judgement Treat with oral amoxicillin or (doxycycline or clarithromycin if hypersensitive).	Use CURB65 or PSI score to guide Outpatient treatment Stratify by risk for drug resistant *S. pneumoniae* Low risk: Treat with macrolide or doxycycline High risk: Treat with respiratory fluoroquinolone or b-lactam+macrolide	Use CRB65 to guide Outpatient treatment Treat with one of: aminopenicillin ± macrolide Aminopenicillin/b-lactamase inhibitor ± macrolide Non-antipseudomonal cephalosporin Cefotaxime or ceftriaxone ± macrolide Levofloxacin Moxifloxacin Penicillin g ± macrolide

*These are not necessarily the terms used in the guidelines but give a broad translation of what the guidelines state.

Khan & Woodhead, F1000 Prime Rep. 2013;;5:43
Free access: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3790563/pdf/medrep-05-43.pdf

Note: *S. pneumoniae* is (probably) the most frequent isolated organism in CAP (~ 20 %), but others may need to be considered (*Mycoplasma pneumoniae* ~ 11 %; *Chlamydia pneumoniae* ~ 8.0 %; *Haemophilus influenzae* ~ 3.3 %), and ~ 50% of cases remain without successful isolation

(Woodhead. Eur Respir J 2002; 36:20s-27s)

S. aureus in Asia: VISA and hVISA

- VRSA and true VISA are rare[1]
- hVISA phenotype is much more frequent
  - 1/3 of MRSA isolates in Korea and was independently associated with a vancomycin MIC ≥2 mg/L and rifampicin resistance[2]
- VISA and hVISA are associated with a longer period of prior glycopeptide use, bone/joint and prosthetic infections, and treatment failure[3]

hVISA heterogeneous vancomycin-intermediate-resistant *S. aureus* :
VISA: vancomycin-intermediate *S. aureus*
VRSA vancomycin-resistant *S. aureus*
MRSA methicillin-resistant *S. aureus*

1. Kang & Song. *Infect Chemother.* 2013;45:22-31
2. Park, *et al. J Antimicrob Chemother*. 2012;67:1843-9
3. Fong, *et al. Eur J Clin Microbiol Infect Dis.* 2009;28:983-7

S. Aureus in Asia:

- VRSA and true VISA are r
- hVISA is much
- VISA and hVISA are asso

higher trough levels may be necessary

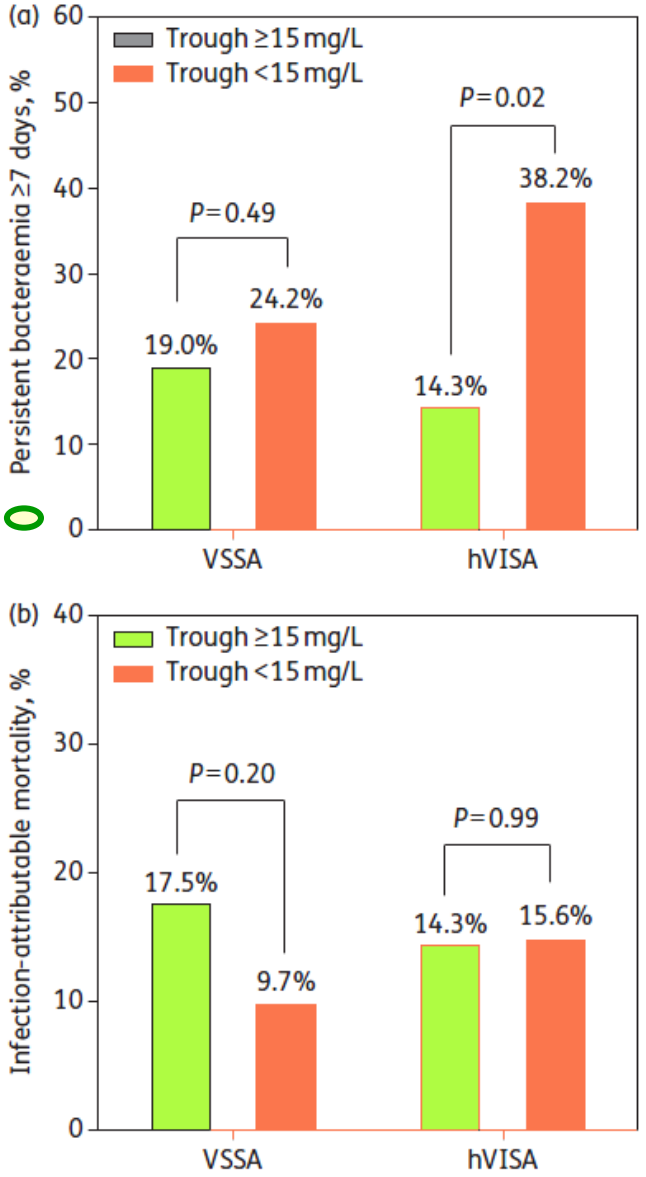


Figure 1. Clinical outcomes of patients with hVISA and VSSA bacteraemia based on initial vancomycin trough levels.

1. Kang & Song Infect Chemother 2013;45:22-31
2. Park *et al* J Antimicrob Chemother 2012;67:1843-9.
3. Fong *et al* Eur J Clin Microbiol Infect Dis 2009;28:983-7.
4. Park *et al* J Antimicrob Chemother. 2012;67:1843-9.

Park, *et al.* JAC. 2012;67:1843-9

S. aureus in Africa

- Very little is known about Africa !
- But data that are coming are challenging…

Infection
DOI 10.1007/s15010-014-0589-1

REVIEW

Methicillin-resistant *Staphylococcus aureus* as a cause of invasive infections in Central Africa: a case report and review of the literature

M. A. M. Huson · R. Kalkman · J. Remppis · J. O. Beyeme · C. Kraef · F. Schaumburg · A. S. Alabi · M. P. Grobusch

Infection. 2014 Jan 25. [Epub ahead of print]

S. aureus in Africa

- Very lit
- But da

Infection
DOI 10.1007/s15010-014-0589-1

REVIEW

Methicillin-resis infections in Ce of the literature

M. A. M. Huson · R. Kall
J. O. Beyeme · C. Kraef ·
A. S. Alabi · M. P. Grobu

Infection. 2014 Jan 2

Table 1 Epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) in Central Africa

Country[a]	References	Study period	Type of specimens	Setting	Total number of isolates screened	Total number of *S. aureus* isolates	MRSA isolates (%)[b]
Cameroon	Kesah et al. [30]	1996–1997	Clinical isolates: including surgical samples (swabs and pus), ear, nose, and throat samples, urine, sputum, cerebrospinal fluid, aspirates, and blood cultures	Urban, university hospital	Not indicated	127	27 (21.3)
	Breurec et al. [31]	January 2007–March 2008	Clinical isolates from patients with suspected staphylococcal infection	Urban, university hospital	Not indicated	32	9 (28.1)
Gabon	Schaumburg et al. [33]	2008–2010	Healthy volunteers: isolates from anterior nares, the axilla, and groin	Semi-urban	Not indicated	163	6 (3.7)
			Clinical isolates: mainly wound infection, bacteremia, and abscesses	Semi-urban, regional referral hospital	Not indicated	54	6 (11.1)
	Schaumburg et al. [36]	2009	Healthy volunteers: nasal carriage	Remote rural	100	34	0
	Ateba Ngoa et al. [32]	February–July 2009	Asymptomatic volunteers[c]: isolates from anterior nares, the axilla, and groin	Rural and semi-urban	500	146	5 (3.4)
	Alabi et al. [34]	January 2009–September 2012	Clinical isolates: mainly bloodstream, ear-eye-nose-throat, and skin and soft tissue infection	Semi-urban, regional referral hospital	Not indicated	328	19 (5.8)
	Schaumburg et al. [35]	March 2010–January 2013	Healthy mothers (nares, mamillae) and infants (nares, throat)	Rural	Not indicated	474	9 (1.9)

[a] No data were available for countries other than Cameroon and Gabon

[b] Percentage of the total *S. aureus* isolates

[c] 198 inpatients asymptomatic for *S. aureus*-related disease and 302 healthy volunteers

S. aureus in Africa

- Very little is known about Afric
- But data that are coming are c

Infection
DOI 10.1007/s15010-014-0589-1

REVIEW

Methicillin-resistant *Staphylococcus aureus* as a c infections in Central Africa: a case report and re of the literature

M. A. M. Huson · R. Kalkman · J. Remppis · J. O. Beyeme · C. Kraef · F. Schaumburg · A. S. Alabi · M. P. Grobusch

Infection. 2014 Jan 25. [Epub ahead of print]

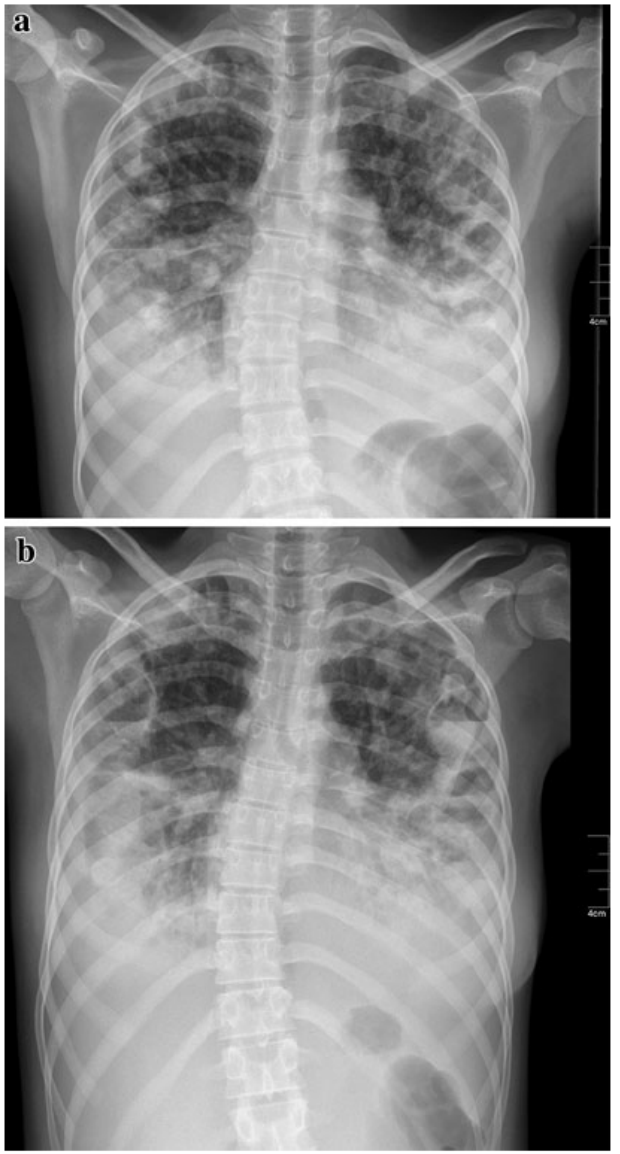


Fig. 1 a Chest X-ray at admission shows bilateral infiltrates and cavitary lesions. b Chest X-ray 6 days after admission demonstrates deterioration of cavitary lesions with air–fluid levels

S. aureus

- **resistant to penicillin, cloxacillin, ciprofloxacin, and erythromycin,**
- **sensitive to gentamicin, clindamycin, trimethoprim–sulfamethoxazole and rifampicin.**

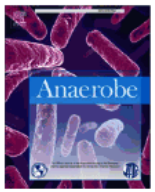
Anaerobes and pneumonia

Anaerobe 18 (2012) 235–239

Contents lists available at SciVerse ScienceDirect

Anaerobe

journal homepage: www.elsevier.com/locate/anaerobe



Clinical microbiology

Anaerobic bacterial infection of the lung

John G. Bartlett*

Johns Hopkins University, School of Medicine, 1830 East Monument Street, Rm 447, Baltimore, MD 21202, United States

Bartlett. *Anaerobe* 2012;18:235-9

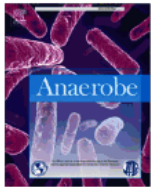
Anaerobes and pneumonia

Anaerobe 18 (2012) 235–239

Contents lists available at SciVerse ScienceDirect

Anaerobe

journal homepage: www.elsevier.com/locate/anaerobe



Clinical microb

Anaerobic

John G. Bartle

Johns Hopkins Universit

Table 2
Clinical features of pulmonary infections involving anaerobic bacteria[a].

Number[b]	Pneumonitis 79	Abscess 83	Empyema 51	Total 213
Age (yrs)	60	52	49	51
Peak fever (°F)	102.6	102.1	102.4	102.4
WBC (× 1000/mL)	13.7	15.0	21.6	15.0
Duration six (days)	3	14	15	7
Weight loss (Yes)	3%	43%	55%	30%
Putrid discharge	4%	49%	63%	32%
Mortality	4%	4%	6%	4%

[a] Categories are mutually exclusive.
[b] All figures are median values.

Bartlett. *Anaerobe* 2012;18:235-9

What are the outcomes of MDR in VAP?

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.

What are the outcomes of MDR in VAP?

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

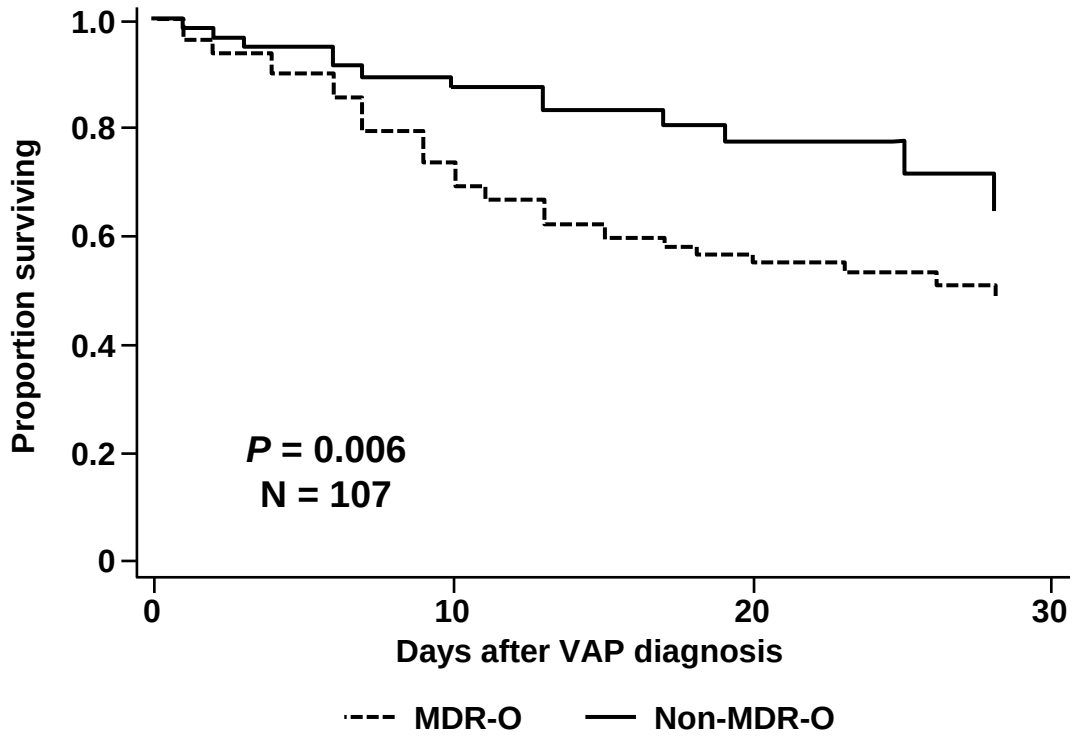
ELSEVIER

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.

What are the outcomes of MDR in VAP?

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

ELSEVIER

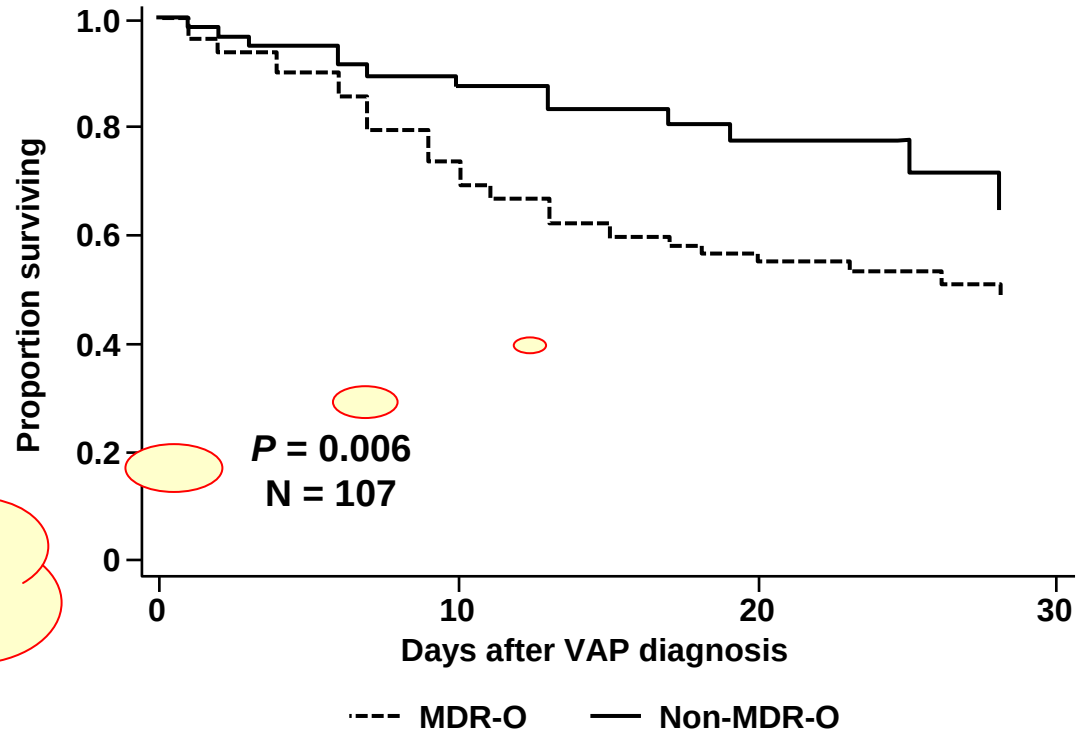
Brief report

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, Ch

I guess such a difference would command a very high price for an anticancer drug...



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.

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

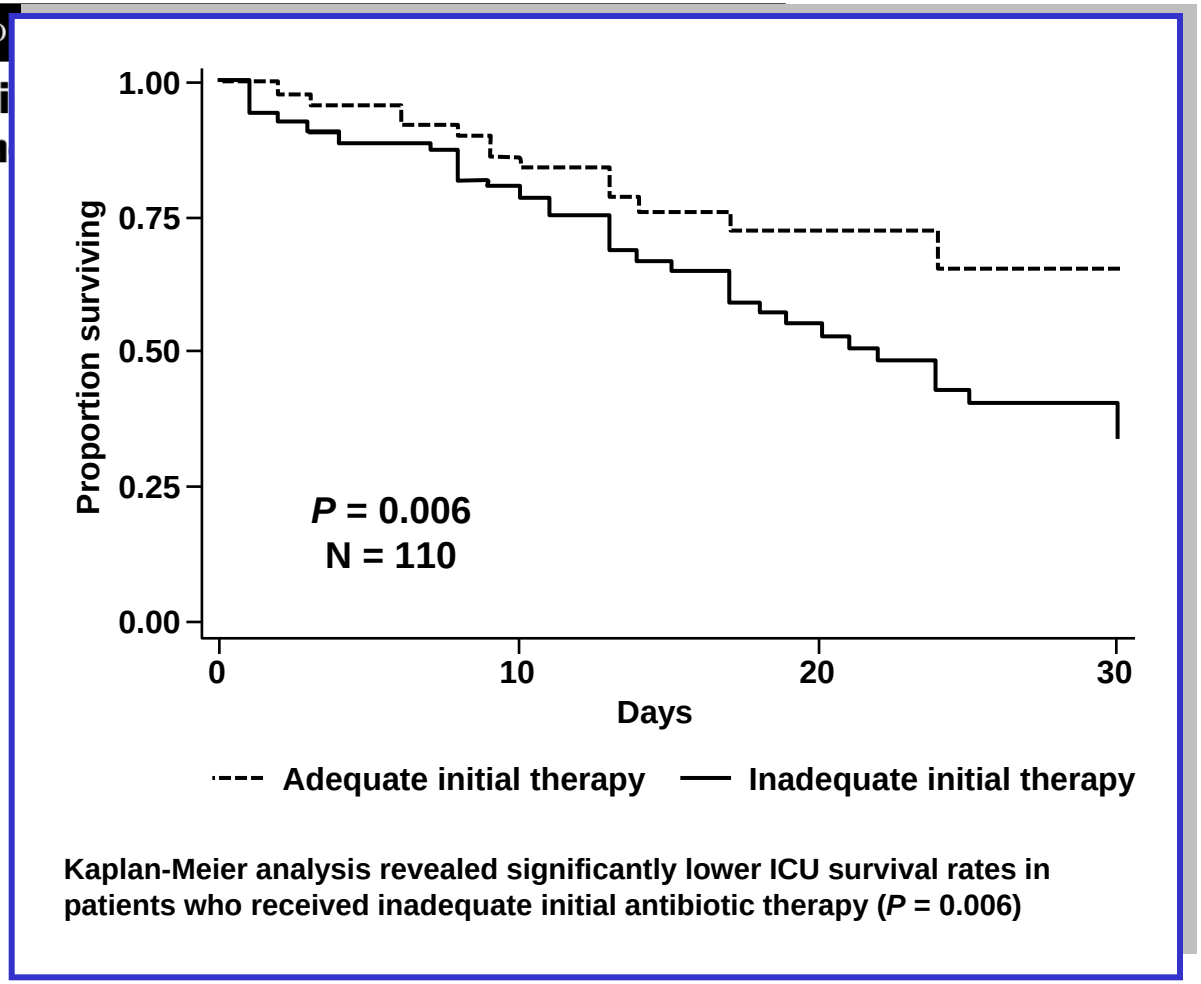
Clinical outcomes of *Pseudomonas aeruginosa* pneumonia in intensive care unit patients

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

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

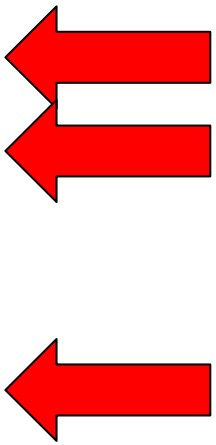


Kaplan-Meier analysis revealed significantly lower ICU survival rates in patients who received inadequate initial antibiotic therapy (*P* = 0.006)

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

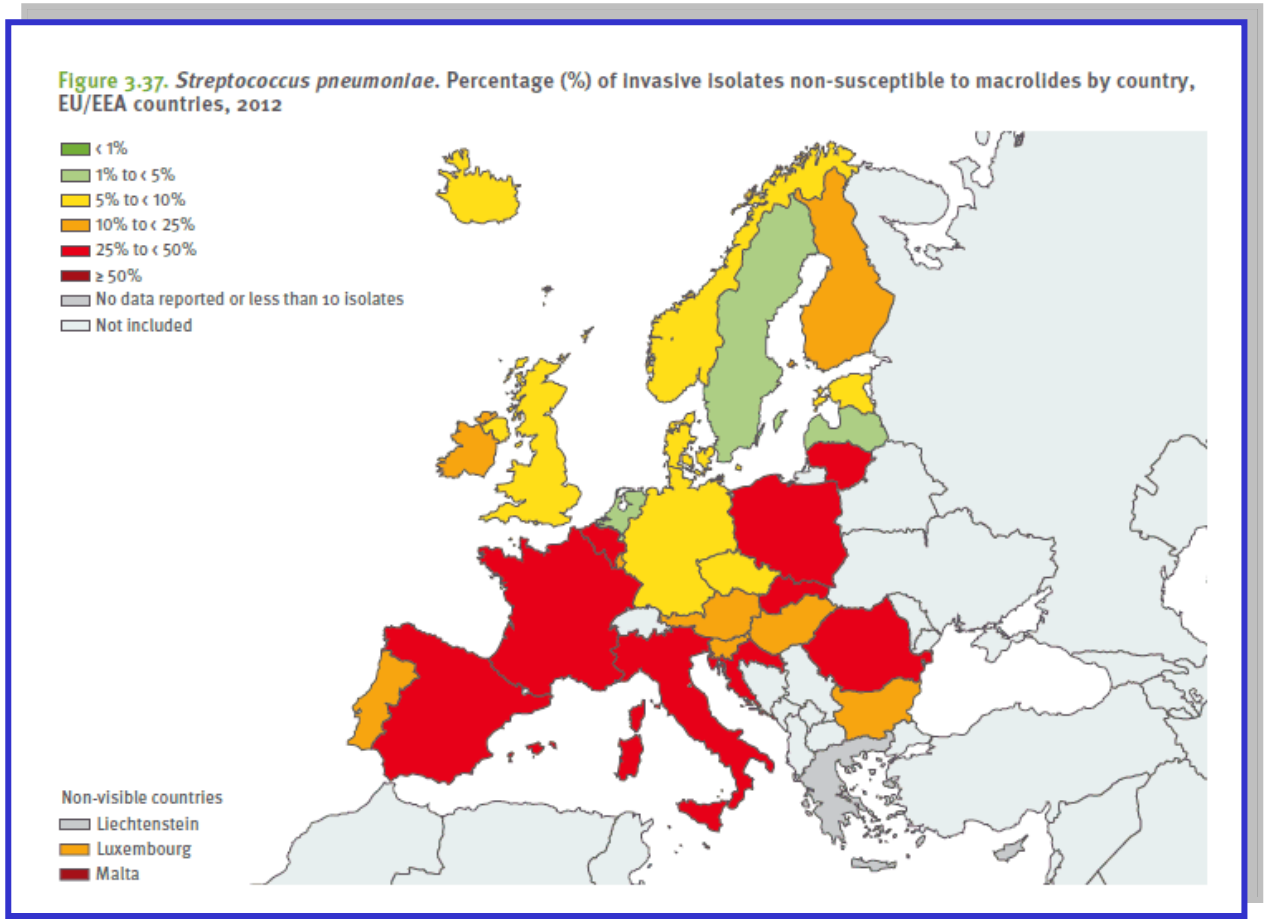
Key questions to ask when setting guidelines in infectious diseases (with application to pneumonia)

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



Some potential approaches

- **Community-acquired pneumonia**
  - **local (country, region...) data on resistance (example: macrolides and *S. pneumoniae*)**



European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2012. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2013. p. 52

Some potential approaches

- **Community-acquired pneumonia**
  - local (country, region...) data on resistance (example: macrolides and *S. pneumoniae*)
  - **stratification for occurrence of resistant pathogens (or with decreased susceptibility [β-lactams])**

Some potential approaches

- **Community-acquired pneumonia**
  - local (country, region...) data on resistance (example: macrolides and *S. pneumoniae*)
  - **stratification for occurrence of resistant pathogens (or with decreased s**

Table 2. Scoring System to Evaluate Presence of MDR Pathogens in Hospitalized Patients With CAP

Variable	Score
No risk factors for MDR pathogen (including comorbidities)	0
≥ 1 of the following: cerebrovascular disease; diabetes; COPD; antimicrobial therapy in preceding 90 days; immunosuppression; home wound care; home infusiontherapy (including antibiotics)	0.5
Residence in a nursing home or extended-care facility	3
Hospitalization for ≥ 2 days in preceding 90 days	4
Chronic renal failure	5

Adapted from Aliberti S, Di Pasquale M, Zanaboni AM, et al. Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. *Clin Infect Dis.* 2012;54(4):470–478.[12] © 2011; Oxford University Press. Used with permission.

Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; MDR, multidrug-resistant.

Alberti & Kaye.*Postgrad Med.* 2013;125:31-42

Some potential approaches

- **Community-acquired pneumonia**
  - local (country, region...) data on resistance (example: macrolides and *S. pneumoniae*)
  - stratification for occurrence of resistant pathogens (or with decreased susceptibility [β-lactams])
  - **scoring of severity and potential for Gram-negatives**

Table 4. Recommended community-acquired pneumonia therapy and management from published international guidelines *

	BTS guidelines [24]	ATS/IDSA guidelines [25]	ERS/ESCMID guidelines [26]
Moderate/high severity patients*	CURB65 score 3 or more consider ICU Treat with β-lactam plus macrolide iv	Consider ICU for sepsis or >2 minor severity criteria Increased Comorbidities or prior antimicrobials (within 3 months) treat with respiratory fluoroquinolone or beta lactam plus macrolide iv	Consider ICU for respiratory failure or sepsis or >2 minor severity criteria Stratify by risk for *Pseudomonas aeruginosa* Non-antipseudomonal treat with cephalosporin III + macrolide Or Moxifloxacin or levofloxacin ± non-antipseudomonal cephalosporin III

*These are not necessarily the terms used in the guidelines but give a broad translation of what the guidelines state.

Khan & Woodhead . F1000 Prime Reports 2013;5:43

Some potential approaches

- **Community-acquired pneumonia**
  - local (country, region...) data on resistance (example: macrolides and *S. pneumoniae*)
  - stratification for occurrence of resistant pathogens (or with decreased susceptibility [β-lactams])
  - scoring of severity and potential for Gram-negatives
  - **presence of *S. aureus* (MSSA / MRSA)**

Type of infection	MSSA	MRSA	days
acute / non PVL	• BLRP (150 mg/kg) [a] • amoxyclav (2-6g) • cllindamycin [c]	• vancomycin (30mg/kg) [b] • teicoplanin (400-600 mg/day • clindamycin [c] • pristinamycin	4-7
necrosis / PVL +	• BLRP (150-200 mg/kg) [a] **+** clindamycin [c]	• vancomycin (30-40 mg/kg [b] or continuous infusion) **+** clindamycin [c] • linezolid (1.2g q12h) * • ceftaroline (1.2g) + clindamycin [c] *	≥ 14

[a] β-lactamase-resistant penicillin (in 3 or 4 administrations/day (q8h or Q6h)) ; [b] in 2 administrations per day (q12h) ; [c] 1.8 to 2.4 g/day in 3-4 administration per day (q8h or q6h); * non-validated (off-label)

Translated from Valour *et al* Rev Pneumol Clin. 2013;69:368-82

Some potential approaches

- **Hospital acquired pneumonia (including VAP)**
  - preventive measures (VAP)

Table 1. Effects of the main preventive measures for ventilator-associated pneumonia prevention in randomized controlled studies or last meta-analyses

Intervention	Year, design	Patients (*n*)	RRR of VAP (%)
Reducing the time at risk			
NPPV	2005, meta-analysis (12 studies)	3030	↓ 25%
Preventing endotracheal tube colonization and minimizing contaminated microaspirations			
Silver-coated ET	2008, RCT (54 ICUs)	1509	↓ 36%
Saline instillation before tracheal suctioning	2009, RCT (one ICU)	262	↓ 54%
ET with SSD	2010, meta-analysis (13 RCTs)	2442	↓ 48% (four RCTs)
Endotracheal tube with ultrathin membrane and SSD	2007, RCT (one ICU)	280	↓ 64%
Endotracheal tube with an ultrathin and tapered-shape cuff membrane	2008, RCT (one ICU)	134	↓ 45%
Continuous control of tracheal cuff pressure	2011, RCT (one ICU)	122	↓ 63%
Head-of-bed elevation	1999, RCT (two ICUs)	86	↓ 78%
Kinetic beds	2006, meta-analysis (15 RCTs)	1169	↓ 53% (10 RCTs)
Positive end-expiratory pressure	2008, RCT (three ICUs)	131	↓ 63%
Modulation of colonization			
Oral care with chlorhexidine	2010, meta-analysis (12 RCTs)	2341	↓ 24%
Probiotics	2010, RCT (one ICU)	146	↓ 47%

Data from [17]. ET, endotracheal tube; NPPV, noninvasive positive pressure ventilation; RCT, randomized controlled trial; RRR, relative risk reduction; SBT spontaneous breathing trial; SSD, subglottic secretion drainage; VAP, ventilator-associated pneumonia.

Barbier *et al*. *Curr Opin Pulm Med.* 2013;19:216-28

Some potential approaches

- **Hospital acquired pneumonia (including VAP)**
  - guidelines: 1. target organisms

Table 3. Current guidelines for the empirical treatment of hospital-acquired pneumonia, including ventilator-associated pneumonia

	Early-onset HAP/VAP (≤Day 4 of hospital stay/MV) without risk factors for MDR pathogen[a]	Late-onset HAP/VAP (≥Day 5 of hospital stay/MV) OR presence of ≥1 risk factor for MDR pathogen[b]
Most common (i.e. targeted) pathogens	MSSA	MRSA
	Streptococcus pneumonia and other streptococci *Haemophilus* sp.	*Pseudomonas aeruginosa*
	Wild-type *Enterobacteriaceae*	Drug-resistant *Enterobacteriacae*
		Acinetobacter baumannii
		Stenotrophomonas maltophilia.

Barbier, *et al. Curr Opin Pulm Med*. 2013;19:216-28

Some potential approaches

- **Hospital acquired pneumonia (including VAP)**
  - guidelines: 2. Societies' recommendations for "early onset" HAP/VAP without risk factors for MDR pathogen (*)

British Society of Antimicrobial Chemotherapy (2008)	American Thoracic Society/Infectious Diseases Society of America (2005)	European RespiratorySociety/ European Society of Clinical Microbiology and Infectious Diseases/European Society of Intensive Care Medicine (2009)
• aminopenicillin/beta-lactamase inhibitor, **or** • cefuroxime	• ceftriaxone, **or** • levofloxacin, moxifloxacin, or ciprofloxacin, **or** • ampicillin/sulbactam, **or** • ertapenem	• ampicillin/sulbactam or amoxicillin/clavulanate, **or** • cefuroxime, cefotaxime or ceftriaxone, **or** • moxifloxacin or levofloxacin (not ciprofloxacin)

*** add vancomycin or linezoid if MRSA is suspected**

Adapted from Barbier, *et al. Curr Opin Pulm Med*. 2013;19:216-28
See also *Am J Respir Crit Care Med*. 2005;171:388–416 / *JAC*. 2008;62:5–34 / *Intensive Care Med* 2009; 35:9–29

Some potential approaches

- **Hospital acquired pneumonia (including VAP)**
  - guidelines: 2. Societies' recommendations for "late onset" HAP/VAP or with ≥1 risk factors for MDR pathogen

British Society of Antimicrobial Chemotherapy (2008)	American Thoracic Society/Infectious Diseases Society of America (2005)	European RespiratorySociety/ European Society of Clinical Microbiology and Infectious Diseases/European Society of Intensive Care Medicine (2009)
early onset with risk MDR • ceftaxime or ceftriaxone **or** • fluoroquinolone **or** • piperacillin/tazobactam	• cefepime or ceftazidime, **or** • imipenem or meropenem, **or** • piperacillin/tazobactam, **or** • ciprofloxacin or levofloxacin **or** • amikacin or gentamicin or tobramycin	• ceftazidime **or** • imipenem or meropenem **or** • piperacillin/tazobactam + ciprofloxacin or levofloxacin
late onset • use local epidemiology • if *P.aeruginosa*: ceftazidime, ciprofloxacin, meropenem or piperacillin/tazobactam		

*** add vancomycin or linezoid if MRSA is suspected**

Adapted from Barbier *et al* Curr Opin Pulm Med. 2013;19:216-28
See also *Am J Respir Crit Care Med* 2005;171:388–416 / JAC. 2008;62:5–34 / *Intensive Care Med.* 2009; 35:9–29

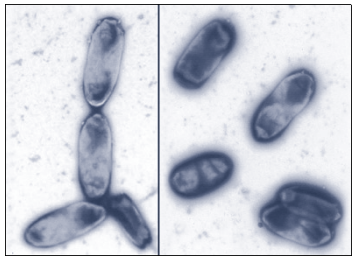
Guidelines: Local vs General

- The empiric algorithm derived from analysis of local microbiologic data predicted significantly better coverage than one defined by an unmodified guideline-driven approach for early HAP/VAP. Our locally-derived TICU algorithm of ceftriaxone+vancomycin for early pneumonia and piperacillin-tazobactam+vancomycin for late pneumonia optimizes the adequacy of initial therapy. Understanding local patterns of pneumonia ensures the creation and maintenance of empiric algorithms that achieve the best clinical outcomes.

Becher RD, Hoth JJ, Rebo JJ, Kendall JL, Miller PR. Locally derived versus guideline-based approach to treatment of hospital-acquired pneumonia in the trauma intensive care unit. *Surg Infect (Larchmt)*. 2012 Dec;13(6):352-9. doi: 10.1089/sur.2011.056. PubMed PMID: 23268613.

1: Dalhoff K, Abele-Horn M, Andreas S, Bauer T, von Baum H, Deja M, Ewig S, Gastmeier P, Gatermann S, Gerlach H, Grabein B, Höffken G, Kern WV, Kramme E, Lange C, Lorenz J, Mayer K, Nachtigall I, Pletz M, Rohde G, Rosseau S, Schaaf B, Schaumann R, Schreiter D, Schütte H, Seifert H, Sitter H, Spies C, Welte T; German Society for Anaesthesiology and Intensive Care Medicine; German Society for Infectious Diseases; German Society for Hygiene and Microbiology; German Respiratory Society; Paul-Ehrlich-Society for Chemotherapy. [Epidemiology, diagnosis and treatment of adult patients with nosocomial pneumonia. S-3 Guideline of the German Society for Anaesthesiology and Intensive Care Medicine, the German Society for Infectious Diseases, the German Society for Hygiene and Microbiology, the German Respiratory Society and the Paul-Ehrlich-Society for Chemotherapy]. Pneumologie. 2012 Dec;66(12):707-65. doi: 10.1055/s-0032-1325924. Epub 2012 Dec 6. German. PubMed PMID: 23225407. https://www.thieme-connect.com/DOI/DOI?10.1055/s-0032-1325924

Haemophilus*:* is it important ?



http://www.pathologyoutlines.com/topic/lymphnodeshinfluenzae.html

- Haemophilus is often considered as a colonizer of the upper respiratory tract with risks only for patients with COPD
- However, in coinfection with a preceding viral infection, Haemophilus may colonize the lung, leading to lethal secondary bacterial pneumonia.

Genome-wide fitness profiling reveals adaptations required by *Haemophilus* in coinfection with influenza A virus in the murine lung

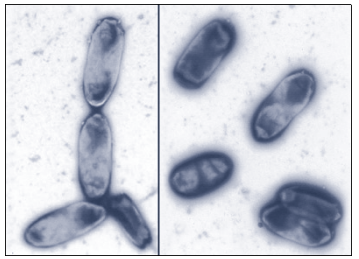
Sandy M. Wong[a], Mariana Bernui[b], Hao Shen[b,1], and Brian J. Akerley[a,1]

[a]Department of Microbiology and Physiological Systems, University of Massachusetts Medical School, Worcester, MA 01605; and [b]Department of Microbiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104

COPD: chronic obstructive pulmonary disease

Wong SM, *et al. Proc Natl Acad Sci U S A.* 2013;110:15413-8.

Haemophilus: this may be why !



http://www.pathologyoutlines.com/topic/lymphnodeshinfluenzae.html

- *Haemop*
  with risk
- Howeve
  colonize

Genome-w
required b
influenza

Sandy M. Wong[a], Mar

[a]Department of Microbiolog
Microbiology, University of

Proc Natl Acad Sci U

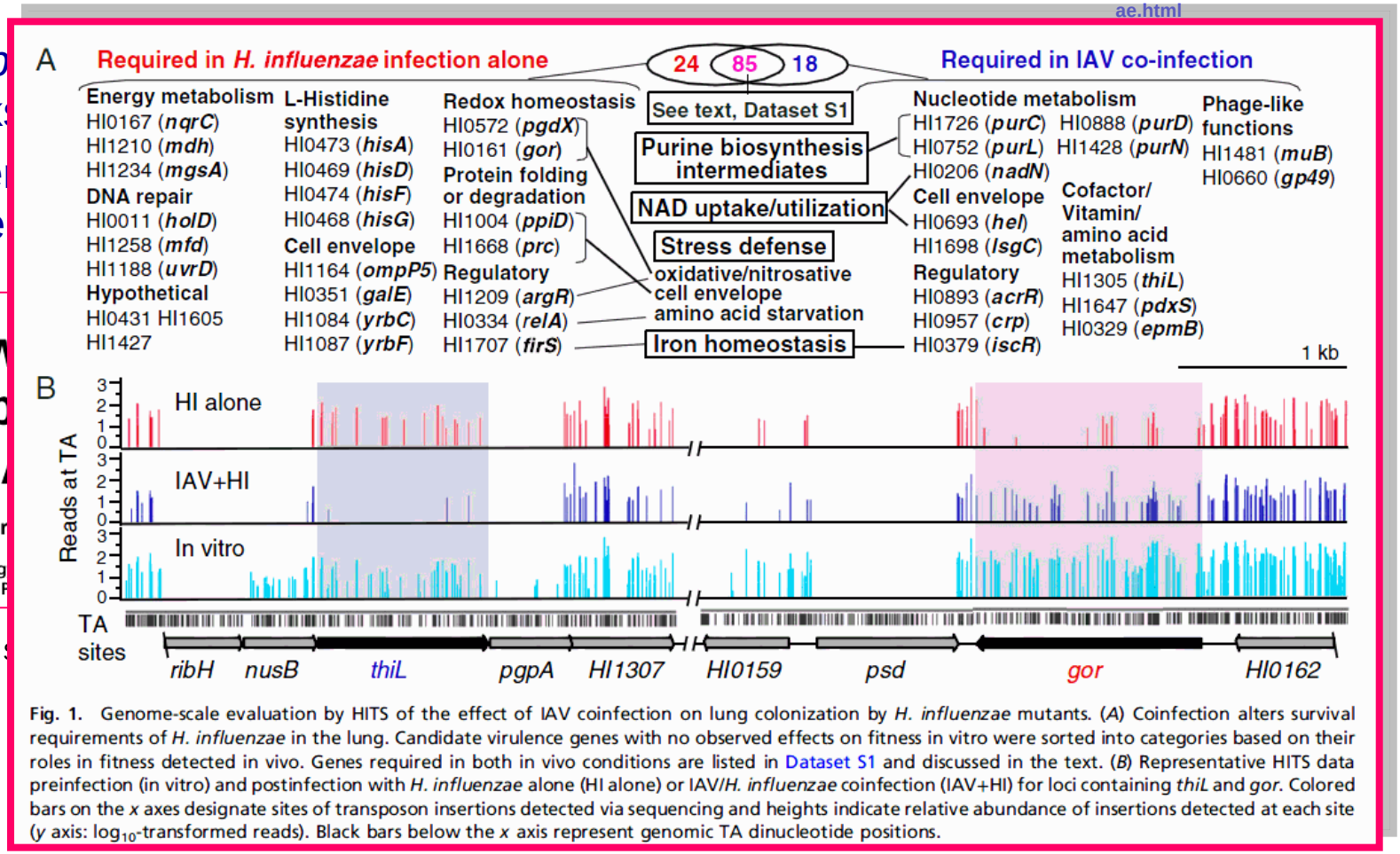
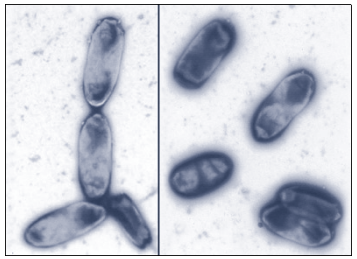


Fig. 1. Genome-scale evaluation by HITS of the effect of IAV coinfection on lung colonization by *H. influenzae* mutants. (*A*) Coinfection alters survival requirements of *H. influenzae* in the lung. Candidate virulence genes with no observed effects on fitness in vitro were sorted into categories based on their roles in fitness detected in vivo. Genes required in both in vivo conditions are listed in Dataset S1 and discussed in the text. (*B*) Representative HITS data preinfection (in vitro) and postinfection with *H. influenzae* alone (HI alone) or IAV/*H. influenzae* coinfection (IAV+HI) for loci containing *thiL* and *gor*. Colored bars on the *x* axes designate sites of transposon insertions detected via sequencing and heights indicate relative abundance of insertions detected at each site (*y* axis: $\log_{10}$-transformed reads). Black bars below the *x* axis represent genomic TA dinucleotide positions.

Wong SM, *et al. Proc Natl Acad Sci U S A.* 2013;110:15413-8.

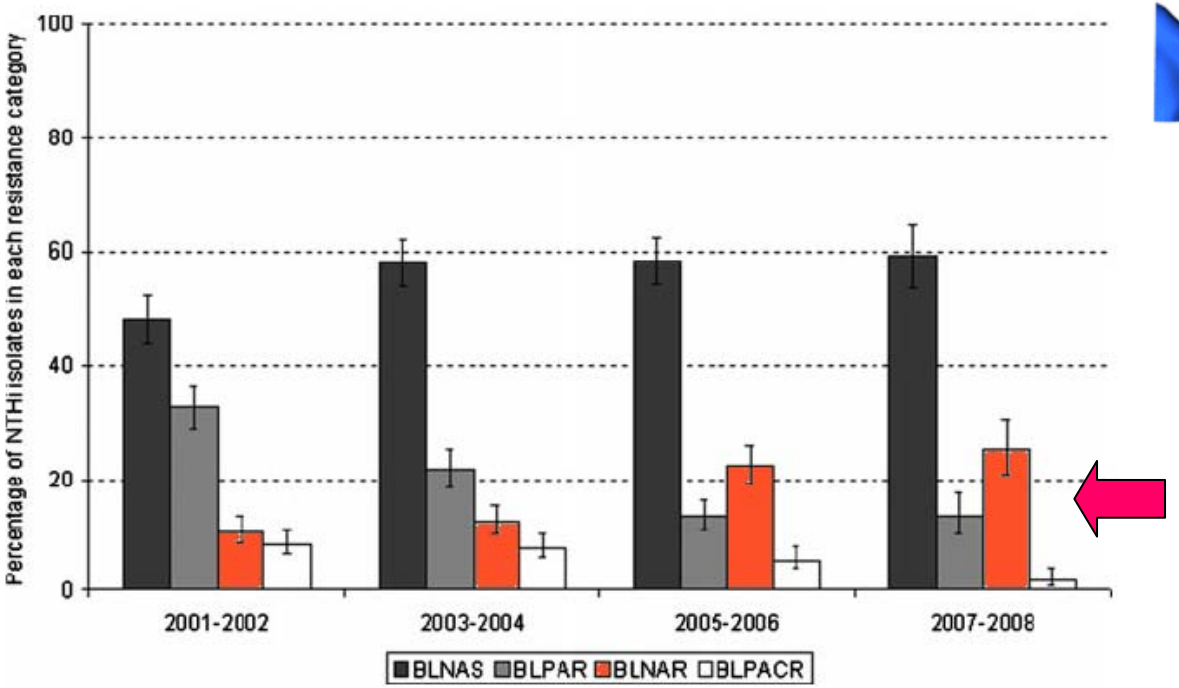
Haemophilus and resistance: recto



http://www.pathologyoutlines.com/topic/lymphnodeshinfluenzae.html

Are -lactamase-negative ampicillin-resistant (BLNAR) isolates important ?

Fig. 1 Evolution of β-lactam resistance of all NTHi strains isolated from children aged 5 years or less in France, from 2001 to 2008. *NTHi*=non-typeable *Haemophilus influenzae*; *BLNAS* = β-lactamase-negative ampicillin-susceptible; *BLPAR* = β-lactamase-positive ampicillin-resistant; *BLNAR* = β-lactamase-negative ampicillin-resistant; *BLPACR* = β-lactamase-positive amoxicillin–clavulanic acid-resistant

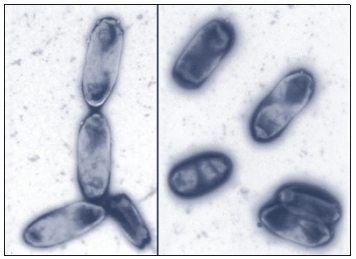


Dabernat *et al. Eur J Clin Microbiol Infect Dis*. 2012;31:2745-53

Warning: antibiotic discs may fail to fully separated between BLNAS and BLNAR populations
(Garcia-Cobos, *et al. JAC*. 2013;68: 159–63)

Good news: The majority of invasive *H. influenzae* including BLNAR remain susceptible to third-generation cephalosporins
(Garcia-Cobos, *et al. JAC*. 2014;69:111-6)
See also Puig, *et al PLoS One*. 2013;13-8:e82515 for clinical success with ceftriaxone and fluoroquinolones

Haemophilus and resistance: verso



http://www.pathologyoutlines.com/topic/lymphnodeshinfluenzae.html

But other regions may be spared

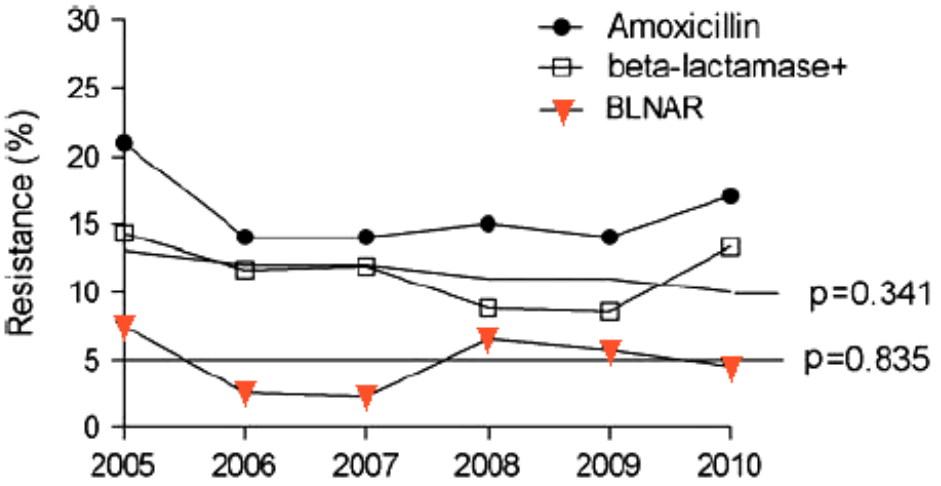
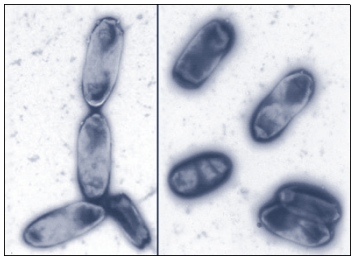


Figure 3. Beta-lactamase-positive and BLNAR isolates over a 6-y period. Division of amoxicillin-resistant strains into BLNAR isolates and beta-lactamase-positive isolates. BLNAR prevalence was approximately 5% over the 6 y and trend analysis showed a stable trend over time. The prevalence of beta-lactamase-positive isolates was approximately 11% over the studied time period. The logistic regression trend line showed a decrease over time, although no statistical difference over time was detected ($p = 0.341$).

Geelen, *et al*. Scand J Infect Dis. 2013;45:606-11.

Haemophilus and fluoroquinolones



http://www.pathologyoutlines.com/topic/lymphnodeshinfluenzae.html

Asia may be leading…

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original article

A molecular analysis of quinolone-resistant *Haemophilus influenzae*: Validation of the mutations in Quinolone Resistance-Determining Regions

Hisashi Shoji*, Tetsuro Shirakura, Kunihiko Fukuchi, Takahiro Takuma, Hideaki Hanaki, Kazuo Tanaka, Yoshihito Niki

Showa University, School of Medicine, Department of Medicine, Division of Clinical Infectious Diseases, 1-5-8, Hatanodai, Shinagawa, Tokyo, Japan

Shoji H, *et al. J Infect Chemother*. 2014;20:250-5

We confirmed that these five mutations strongly contribute to quinolone resistance and found that the degree of resistance is related to the number of the mutations. In addition, the three strains of 18 susceptible strains (16.7%) also had a single mutation. These strains may therefore be in the initial stage of quinolone resistance. Currently, the frequency of quinolone-resistant *H. influenzae* is still low. However, as has occurred with β-lactams, an increase in quinolone use may lead to more quinolone-resistant strains.