Global Antibiotic Resistance in Respiratory Tract Infections

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OM Pharma

Vietnam Master Class
Geneva, Switzerland 3 June 2013

Do we have a problem ?

Obituary

J.-M. Ghuysen

This man discovered the mode of action of penicillins

Ann. Rev. Biochem. 1979. 48:73–101

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

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

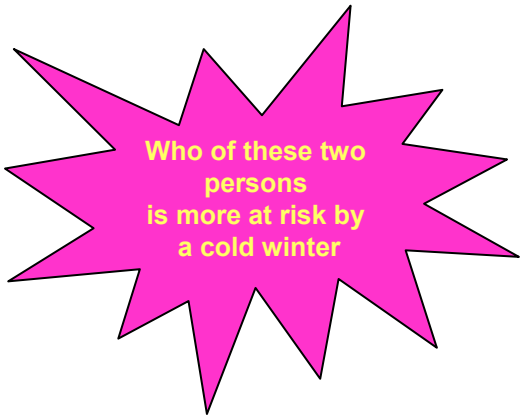
Service de Microbiologie, Faculté de Médecine, Institut de Botanique, Université de Liège, 4000 Sart Tilman, Liège, Belgium

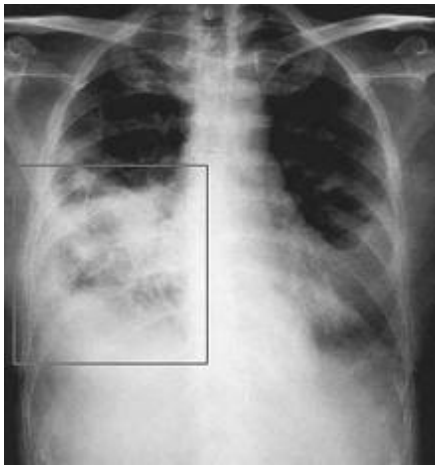
and died from invasive pneumococcal infection …

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

Do we have a problem ?

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





CAP: community acquired pneumonia

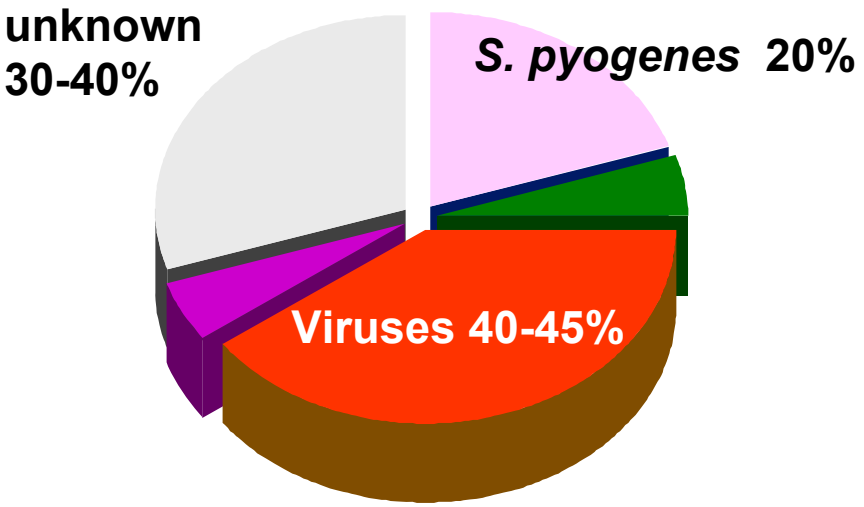
Contents and goals of the presentation

- The diseases and the enemies
  - upper respiratory tract infections
  - lower respiratory tract infections
- Resistance
  - general concepts (resistome, selectome, inappropriate usage)
  - main mechanisms for main bacteria
- Epidemiology
  - main principles and requirements
  - examples with *S. pneumoniae*
  - breakpoints
  - example with *P. aeruginosa*

The diseases and the enemies

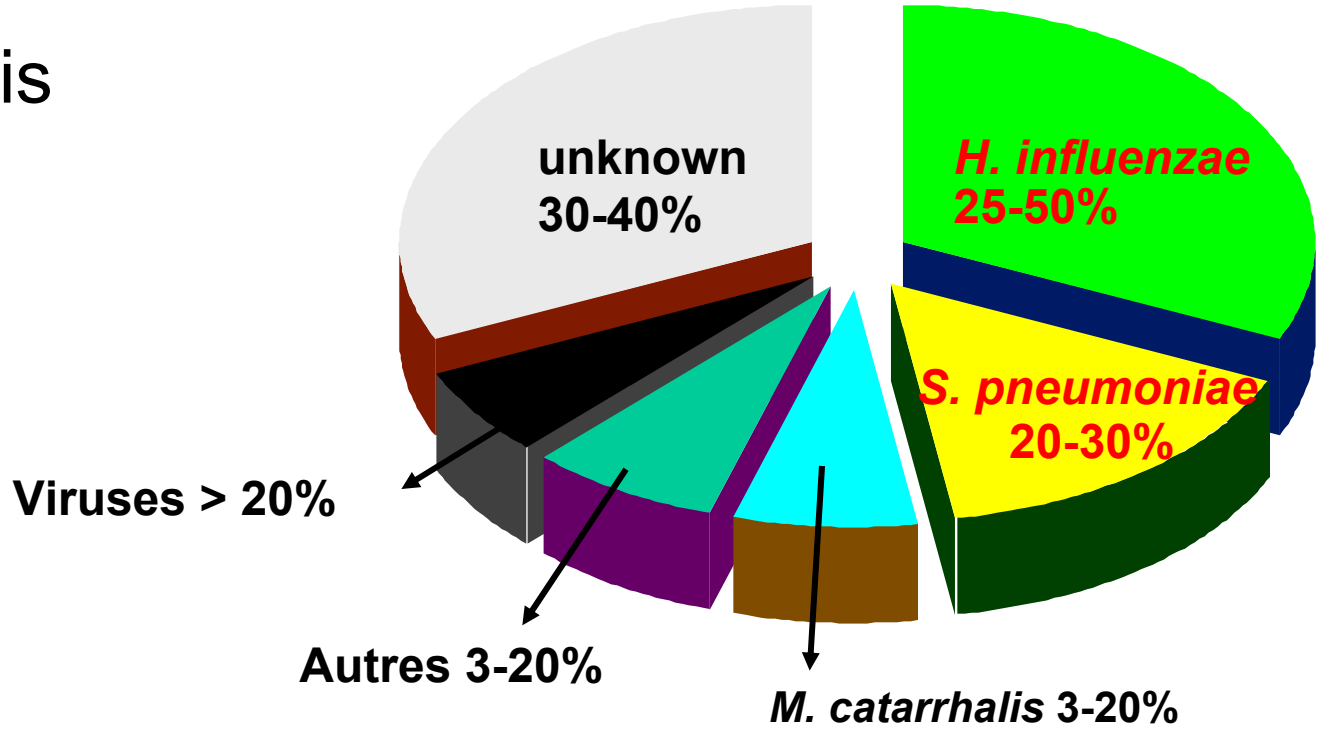
Main pathogens in upper respiratory tract infections

1. pharyngitis



Main pathogens in upper respiratory tract infections

2. otitis

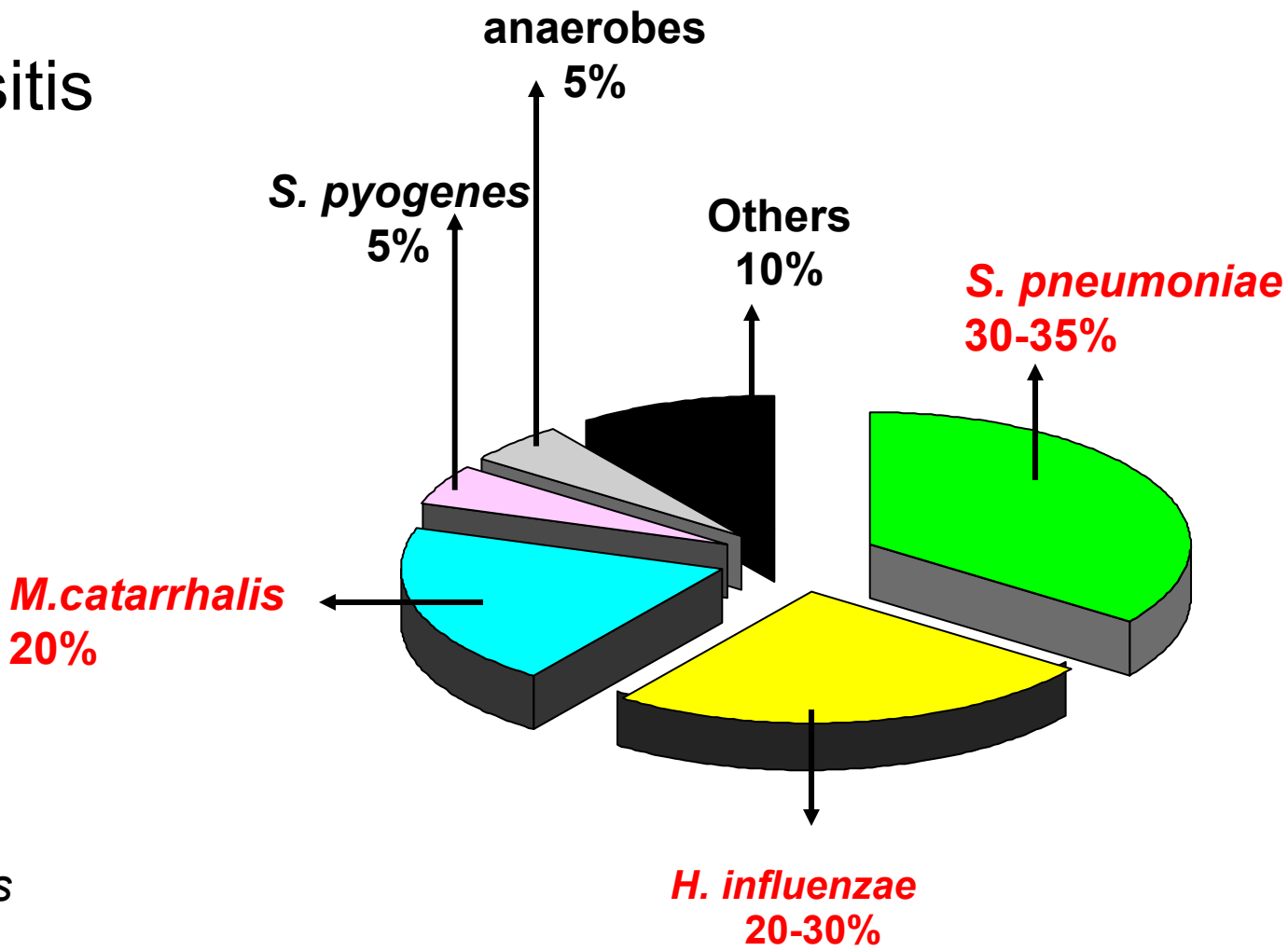


But also:

- *E. coli*; *Pseudomonas*
- *Mycoplasma*, *Chlamydia*

Main pathogens in upper respiratory tract infections

3. sinusitis



But also:

- *S. aureus*

Carriage rate in children with acute upper respiratory tract infection in Ho Chi Minh *

Etiology	No./Total	%
1993		
Pneumococci	70/208	34
Haemophilus influenzae	68/208	33
Hib		2
1996		
Pneumococci	14/51	27.5
Haemophilus influenzae	29/51	56.8
Hib		7.6

Tran *et al*. Pediatr Infect Dis J. 1998 Sep;17(9 Suppl):S192-4. PMID: 9781761

* Pediatric Hospital No. 1 in Ho Chi Minh City (in cooperation with the University Clinic of Pediatrics II at Rigshospitalet in Copenhagen

Main pathogens in lower respiratory tract infections

1. Chronic obstructive lung disease (COPD)

   – **acute exacerbations**
   (at variable frequency – 2 to several fold/year)
   - *Haemophilus influenzae*
   - *Moraxella catarrhalis*
   - *Streptococcus pneumoniae*

   – **if co-morbidities** (diabetes, cardiac insufficiency, ...)
   - *Klebsiella pneumoniae*
   - *Pseudomonas aeruginosa*
   - other Gram-negative bacteria

Main pathogens in lower respiratory tract infections

2. Pneumonia

- **community acquired (CAP)**
  - young adult patients with no risk factor
  - children and elderly
  - comorbidities and severity of disease
- **health care associated**
  - nursing homes
  - hospital
- **immunocompromized patient**
  - asplenic
  - HIV
  - anticancer treatment

Main pathogens in CAP (adult)

Pathogen	Frequency (%)
No pathogen identified	**49.8**
Streptococcus pneumoniae	**19.3**
Viruses	11.7
Mycoplasma pneumoniae	11.1
Chlamydia pneumoniae	8.0
Haemophilus influenzae	3.3
Legionella spp	1.9
Other organisms	1.6
Chlamydia psittaci	1.5
Coxiella burnetii	0.9
Moraxella catarrhalis	0.5
Gram-negative enteric bacteria	0.4
Staphylococcus aureus	0.2

Woodhead M. Eur Respir J Suppl 2002;36:20s-7s.

in Asia, recent reported figures (%) vary from
- 2.2 (China)
- 1 to 23 (Taiwan)
- 1.3 to 20 (Philippines)
- 3.1 to 5.5 (Malaysia)
- 12 (Korea)
- 20.6 to 23.1 (Thailand)
- 35.8 (India)

Jae-Hoon Songa *et al.* Intern. J. Antimicrob. Ag. 38 (2011) 108– 117

In Ho Chi Minh, 71% of pneumonia in children were bacteriemic with *Streptococcus pneumoniae* grown in 92.5% of the blood cultures

Tran *et al.* Pediatr Infect Dis J. 1998 Sep;17(9 Suppl):S192-4.

In Nha Trang, *S. pneumoniae* and *H. influenzae* type b were the most common causes of laboratory-confirmed invasive bacterial disease in children.

Anh *et al.* Clin Infect Dis. 2009 Mar 1;48 Suppl 2:S57-64.

CAP: importance of age, severity of disease and environment on types of bacteria

Pathogen	Frequency (%)
No pathogen identified	**49.8**
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Staphylococcus aureus	0.2

↗ in young adults

↗ in severe cases

↗ in severe cases and comorbidities

↗ in local environments (USA)

Woodhead M. Eur Respir J Suppl 2002;36:20s-7s.

Health-care associated pneumonia

All of the above plus

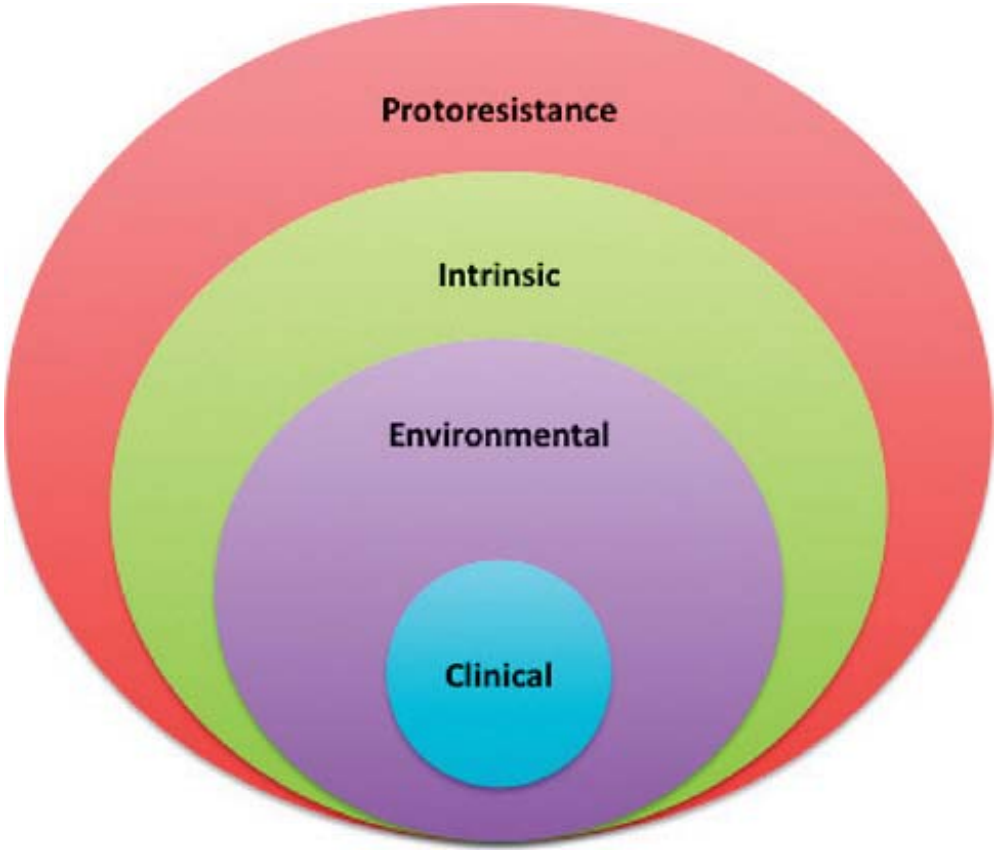
- Gram-positive
  - *S. pneumoniae* (most often multiresistant)
  - Methicillin-resistant *Staphylococci* (includ. *aureus*)
  - Enterococci
- Gram-negative
  - Enterobacterciaceae (*E. coli*, *K. pneumoniae*)
  - *Acinetobacter baumanii*
  - *Pseudomonas aeruginosa*
- Anaerobes

Resistance

Resistance: general concepts

- Mechanisms of resistance are widespread and were most often preexisting the era of clinical use of antibiotics
  - concept of **resistome**
- Resistance is intrinsically inked to antibiotic usage
  - **concept of selectome**
    - no antibiotic → no selection
    - large antibiotic usage in a non-efficient way → high selection
- Resistance **"reservoirs"** are most often not-detected
  - animal reservoirs
  - commensal flora
  - colonization

The resistome …



The antibiotic resistome.

- all the genes and their products that contribute to antibiotic resistance.
- highly redundant and interlocked system
- clinical resistance under represents the resistance capacity of bacteria.
- existing biochemical mechanisms (protoresistome) serve as a deep reservoir of precursors that can be co-opted and evolved to

Antibiotic Resistance:Implications for Global Health and Novel Intervention Strategies: Workshop Summary
http://www.nap.edu/openbook.php?record_id=12925

"Father resistance genes": an original example with aminoglycosides

Proc. Nat. Acad. Sci. USA
Vol. 70, No. 8, pp. 2276–2280, August 1973

Aminoglycoside Antibiotic-Inactivating Enzymes in Actinomycetes Similar to Those Present in Clinical Isolates of Antibiotic-Resistant Bacteria

(streptomyces/origin of R-factors/gentamicin-acetate)

RAOUL BENVENISTE* AND JULIAN DAVIES†

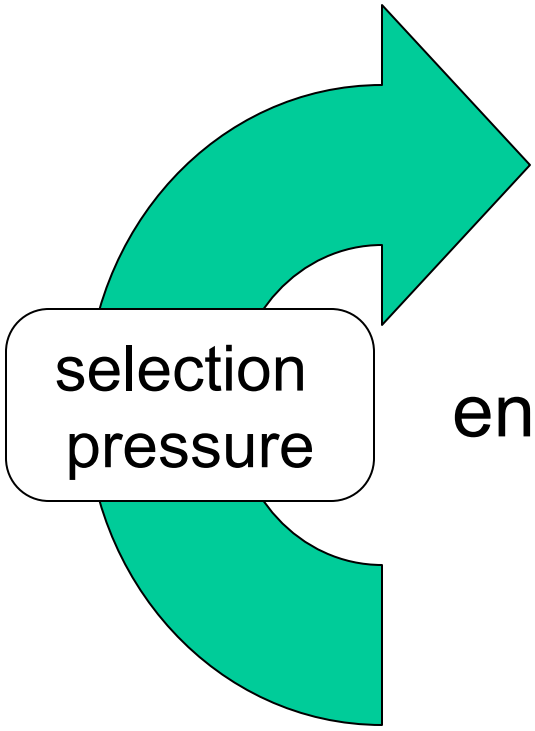
Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin—Madison, Madison, Wis. 53706

Communicated by Henry Lardy, May 11, 1973

One of the most striking properties of the actinomycetes is the extent to which they produce antibiotics; most of the aminoglycoside antibiotics (streptomycin, neomycin, kanamycin, gentamicin, tobramycin, and lividomycin) are produced by them.

The selectome

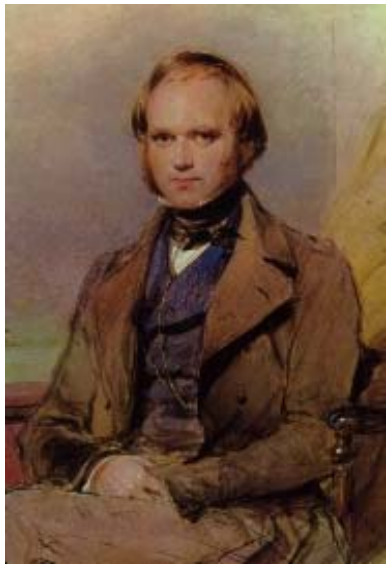
A simple application of Darwin's principles ...



genes

enzymes / nucleoproteins

function

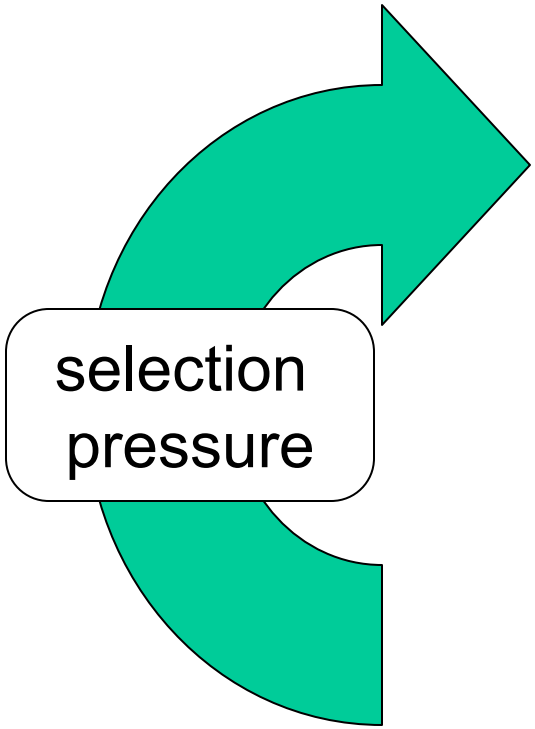


Detail of watercolor by
George Richmond, 1840.
Darwin Museum at Down House

How and why can you select so easily ?

A simple application of Darwin's principle…

to a highly plastic material…



- an infectious focus typicaly contains more than 10^6 - 10^9 organisms
- most bacteria multiply VERY quickly (20 min…) and do mistake …
- they are not innocent or useless mistakes

fast selection of the fittest !

The hidden risk of therapy (in our hospitals …)

International Journal of Antimicrobial Agents 36 (2010) 513–522

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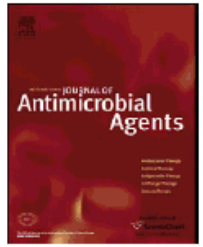
journal homepage: http://www.elsevier.com/locate/ijantimicag

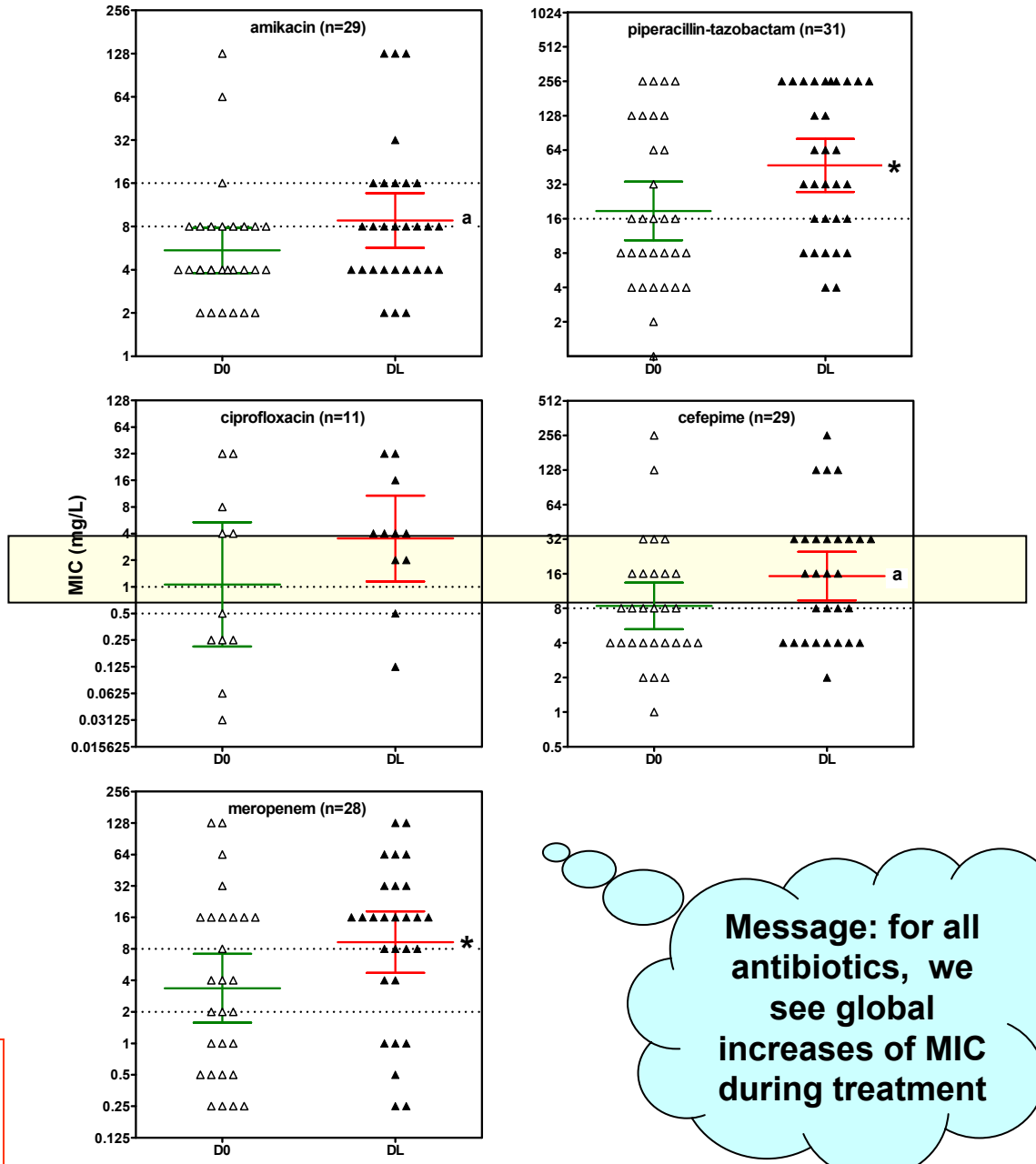


In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou[a,1], Sylviane Carbonnelle[a,2], Laëtitia Avrain[a,b], Narcisa Mesaros[a,3], Jean-Paul Pirnay[c], Florence Bilocq[c], Daniel De Vos[c,d], Anne Simon[e], Denis Piérard[f], Frédérique Jacobs[g], Anne Dediste[h], Paul M. Tulkens[a,*], Françoise Van Bambeke[a], Youri Glupczynski[i]

[a] *Unité de Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium*
[b] *Coris BioConcept, Gembloux, Belgium*
[c] *Laboratory for Molecular & Cellular Technology, Queen Astrid Military Hospital, Neder-over-Heembeek, Brussels, Belgium*
[d] *Department of Molecular and Cellular Interactions, Vrije Universiteit Brussel, Brussels, Belgium*
[e] *Laboratoire de Microbiologie, Cliniques Universitaires St-Luc, Brussels, Belgium*
[f] *Laboratorium voor Microbiologie, Universitair Ziekenhuis Brussel, Brussels, Belgium*
[g] *Clinique des Maladies Infectieuses, Hôpital Erasme, Brussels, Belgium*
[h] *Laboratoire de Microbiologie, Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium*
[i] *Laboratoire de Microbiologie, Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium*

Do you remain effective while treating ?



- 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)

Message: for all antibiotics, we see global increases of MIC during treatment

Actually, selecting for resistance is easy even in a closed system…

Exposure of *E. aerogenes* to anti-Gram (-) β-lactams to 0.25 MIC for 14 days with daily readjustment of the concentration based on MIC determination

strains	Initial		
	MIC (mg/L) [a]		
	TEM	FEP	MEM
2114/2 [c]	8	2	0.25
2502/4 [c]	8	2	0.125
3511/1 [c]	**32**	2	0.125
7102/10 [d]	**512**	**32**	1

[a] figures in bold indicate values > the R breakpoint for Enterobacteriaceae (EUCAST for MEM [8] and FEP [4]; BSAC and Belgium for TEM [16])
[b] dotblot applied with antiOmp36 antibody; signal quantified for grey value after subtraction of the signal of a porin-negative strain (ImageJ software); negative values indicate a signal lower than the background
[c] ESBL TEM 24 (+) ; [d] ESBL (-) and AmpC (+) [high level] ; [e] Intermediate (I) according to EUCAST

Nguyen Thi Thu Hoai *et al*. (post-doc at LDRI)
presented at the 8th ISAAR, Seoul, Korea, 8 April 2011 and additional work in progress at the International University (Vietnam National University) at Ho Chi Minh

A simple experiment …

Exposure of *E. aerogenes* to anrti-Gram (-) β-lactams to 0.25 MIC for 14 days with daily readjustment of the concentration based on MIC determination

strains	Initial			TEM-exposed			Revertant		
	MIC (mg/L) [a]			MIC (mg/L)			MIC (mg/L)		
	TEM	FEP	MEM	TEM	FEP	MEM	TEM	FEP	MEM
2114/2 [c]	8	2	0.25	**2048**	**> 128**	**16**	**32**	4	0.5
2502/4 [c]	8	2	0.125	**8192**	4	0.25	**4096**	1	0.125
3511/1 [c]	**32**	2	0.125	**4096**	**32**	0.125	**4096**	**8**	0.5
7102/10 [d]	**512**	**32**	1	**16384**	**> 128**	4 [e]	**8192**	**64**	1

[a] figures in bold indicate values > the R breakpoint for Enterobacteriaceae (EUCAST for MEM [8] and FEP [4]; BSAC and Belgium for TEM [16])
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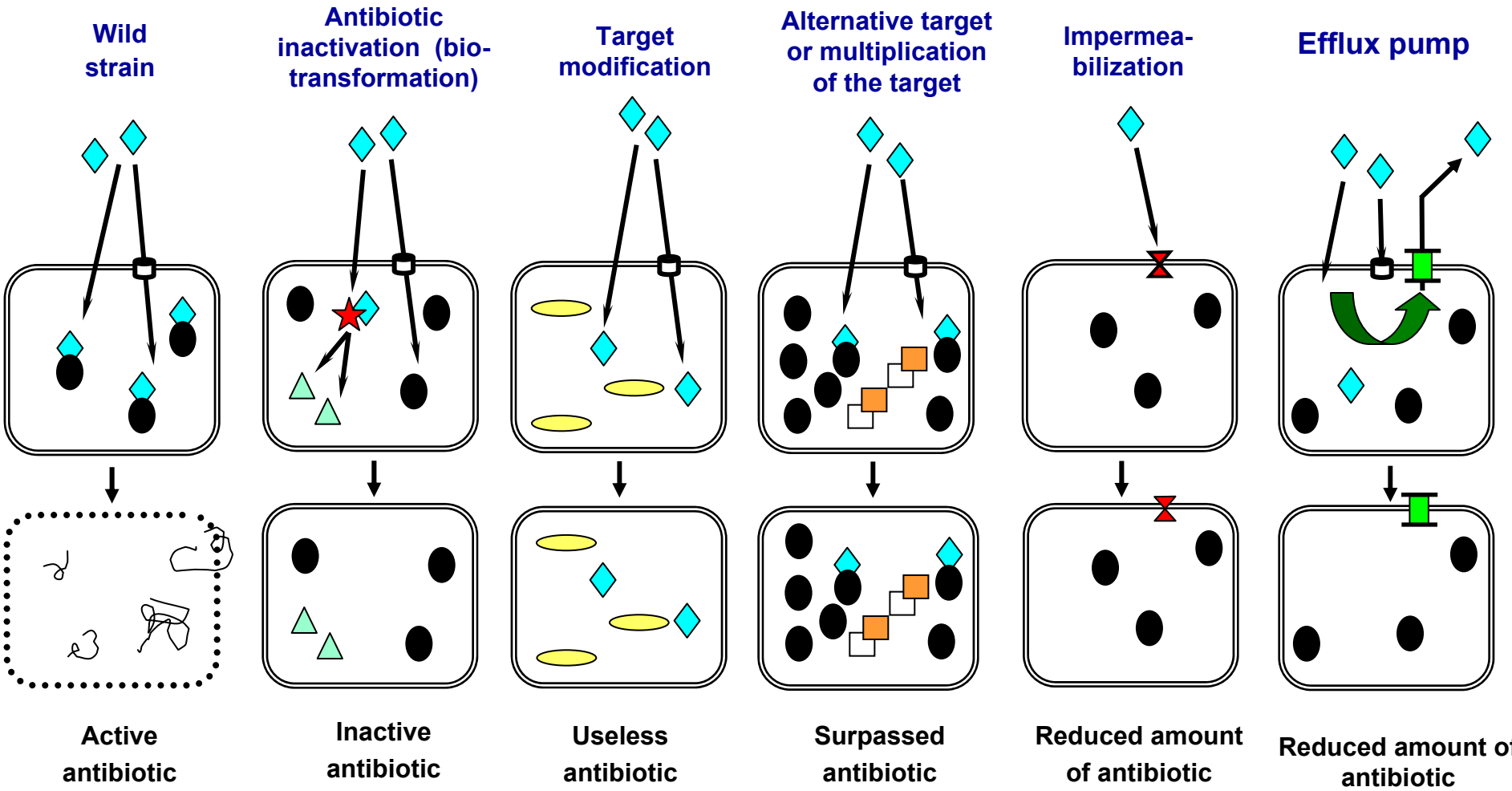
Nguyen Thi Thu Hai *et al*. (post-doc at LDRI) presented at the 8th ISAAR, Jeoju, Korea, 8 April 2011, [illegible] in progress [illegible] at UMP (Vietnam) and Ho Chi Minh

sub-MIC concentrations select for resistance !

Antibiotic resistance: short overview of main mechanisms



Main resistance mechanisms of bacteria of importance in Respiratory Tract Infections and how to fight them

Organism	Mechanism	What to do ?	success ?
Streptococcus pneumoniae	target mutation PBP2x with low penicillin binding	increasing the dosage of β -lactams	partial (MIC $\leq$ 4 mg/L)
	target mutation for macrolides, lincosamides and steptogramins	nothing (high-level resistance)	no
	efflux for macrolides	increase the dose (but difficult) use ketolides or 16-membered macrolides	disputable Telithromycin effective but risk of toxicity
	efflux for fluoroquinolones	avoid fluoroquinolones subject to efflux (ciprofloxacin, gemifloxacin)	yes (if using moxifloxacin)

Main resistance mechanisms of bacteria of importance in Respiratory Tract Infections and how to fight them

Organism	Mechanism	What to do ?	success ?
Haemophilus influenzae	β -lactamase	add a β -lactamase inhibitor	yes (but toxicity)
	target mutation for β -lactams	high level resistance	no
Moraxella catarrhalis	β -lactamase	add a β -lactamase inhibitor	yes (but toxicity)
Staphylococcus aureus	methicillin-resistance	use vancomycin, linezolid, or daptomycin	yes, but limits (vancomycin; daptomycin) and toxicities
Mycoplasma pneumoniae	target mutation for macrolides	nothing (high level resistance)	no

Main resistance mechanisms of bacteria of importance in Respiratory Tract Infections and how to fight them

Organism	Mechanism	What to do ?	success ?
Enterobacteriaceae	β -lactamases (including ESBL and carbapenemases)	change antibiotic(s)	yes (but difficulties in case of MDR)
	target mutations for fluoroquinolones	use the most potent fluoroquinolone (dissociated resistance)	moderate
	efflux (affect several classes)	"fine-tuning" antibiotic choice (based on antibiogram)	moderate

Main resistance mechanisms of bacteria of importance in Respiratory Tract Infections and how to fight them

Organism	Mechanism	What to do ?	success ?
Pseudomonas aeruginosa	β -lactamases (including ESBL)	change antibiotic(s)	yes (but difficulties in case of MDR)
	decreased permeability	choosing an antibiotic with higher permeability	moderate
	target mutations for fluoroquinolones	use the most potent fluoroquinolone (dissociated resistance)	moderate
	efflux (affect several classes)	"fine-tuning" antibiotic choice (based on antibiogram)	moderate

Epidemiology

Epidemiology: principles

Epidemiological (surveillance) studies must be

- **geographically** well adapted to the type of pathogen
  - *S. pneumoniae* → regional or national
  - *P. aeruginosa* → by hospital and even wards
- **comprehensive**
  - correct coverage of patients, underlying diseases, and organisms of interest
  - with a sufficiently large number of isolates in a given period
- use **appropriate interpretative criteria** (breakpoints)

S. pneumoniae: example in Belgium

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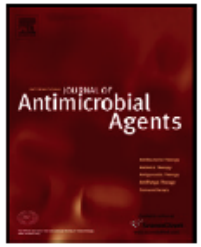
journal homepage: http://www.elsevier.com/locate/ijantimicag



Antimicrobial susceptibility of *Streptococcus pneumoniae* isolates from vaccinated and non-vaccinated patients with a clinically confirmed diagnosis of community-acquired pneumonia in Belgium

Ann Lismond[a], Sylviane Carbonnelle[a,1], Jan Verhaegen[b], Patricia Schatt[c], Annelies De Bel[d], Paul Jordens[e], Frédérique Jacobs[f], Anne Dediste[g], Frank Verschuren[h], Te-Din Huang[i,2], Paul M. Tulkens[a,*], Youri Glupczynski[j], Françoise Van Bambeke[a]

[a] *Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium*
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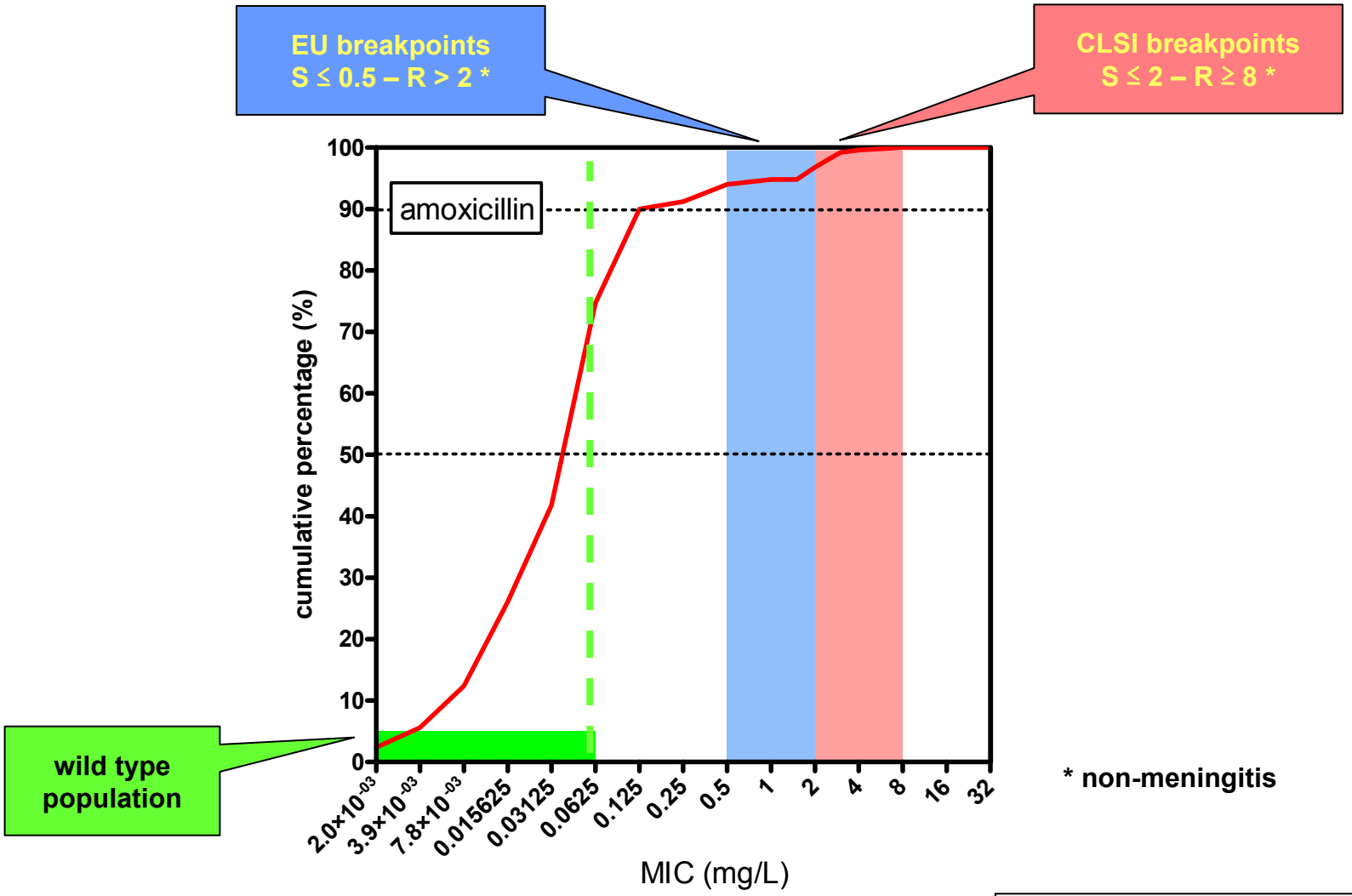
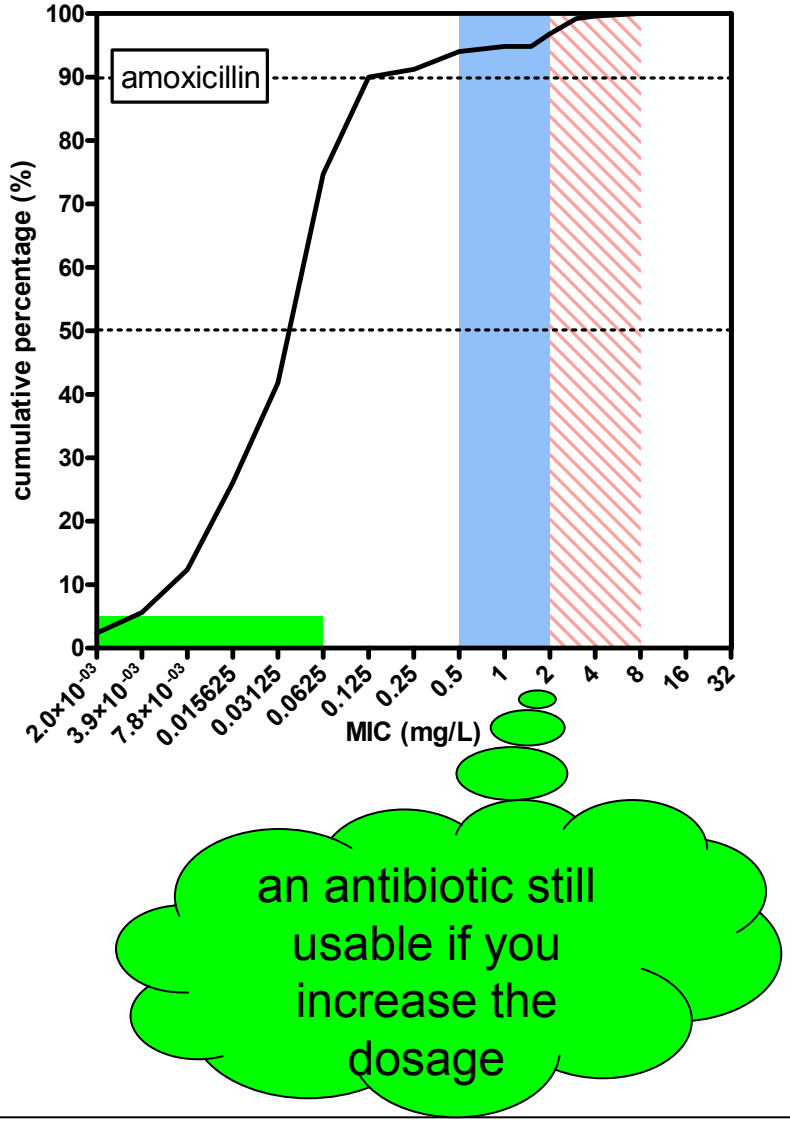
[c] *Laboratoire de microbiologie, Cliniques Notre-Dame de Grâce, Gosselies, Belgium*
[d] *Microbiologie en ziekenhuishygiëne, Universitair Ziekenhuis Brussel, Brussels, Belgium*
[e] *Afdeling pneumologie, O.L.V. Ziekenhuis, Aalst, Belgium*
[f] *Clinique des maladies infectieuses, Hôpital Erasme, Brussels, Belgium*
[g] *Laboratoire de microbiologie, CHU Saint-Pierre, Brussels, Belgium*
[h] *Service des urgences, Cliniques universitaires Saint-Luc, Brussels, Belgium*
[i] *Laboratoire de microbiologie, Cliniques universitaires Saint-Luc, Brussels, Belgium*
[j] *Laboratoire de microbiologie, CHU Mont-Godinne, Yvoir, Belgium*

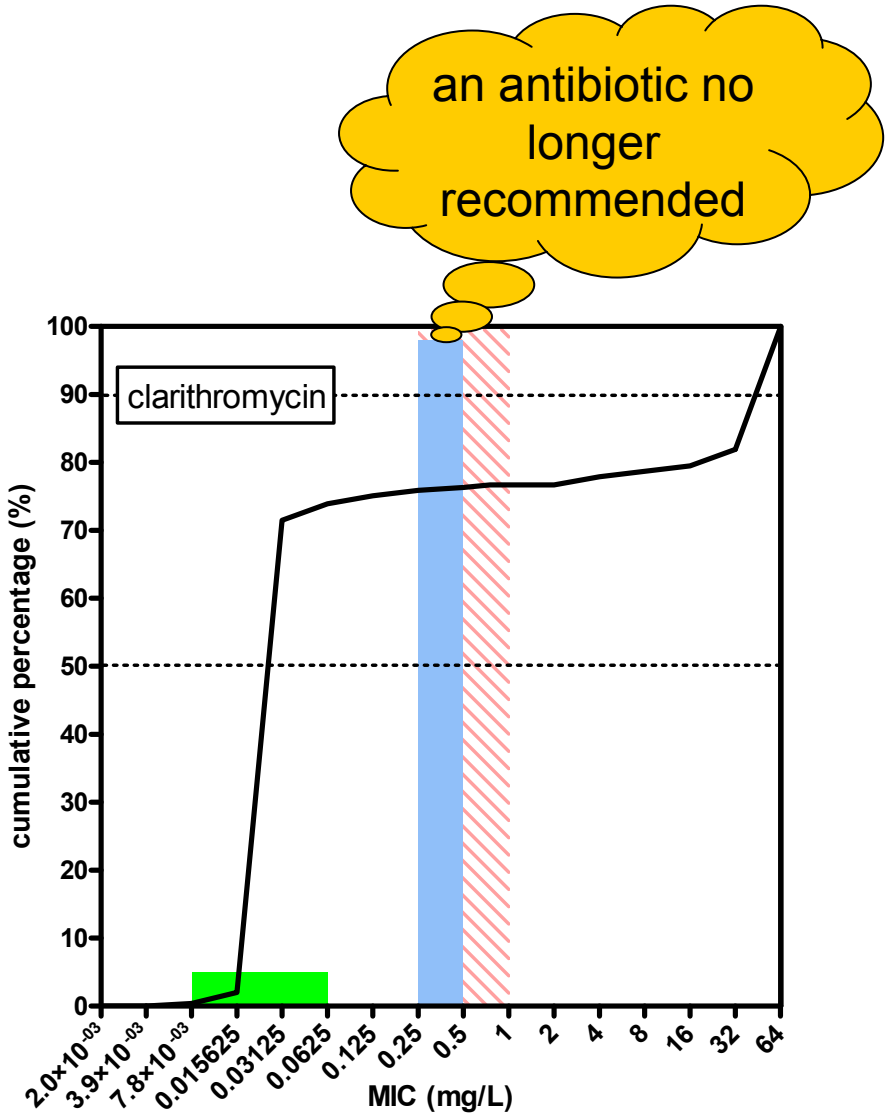
S. pneumoniae: an example in Belgium



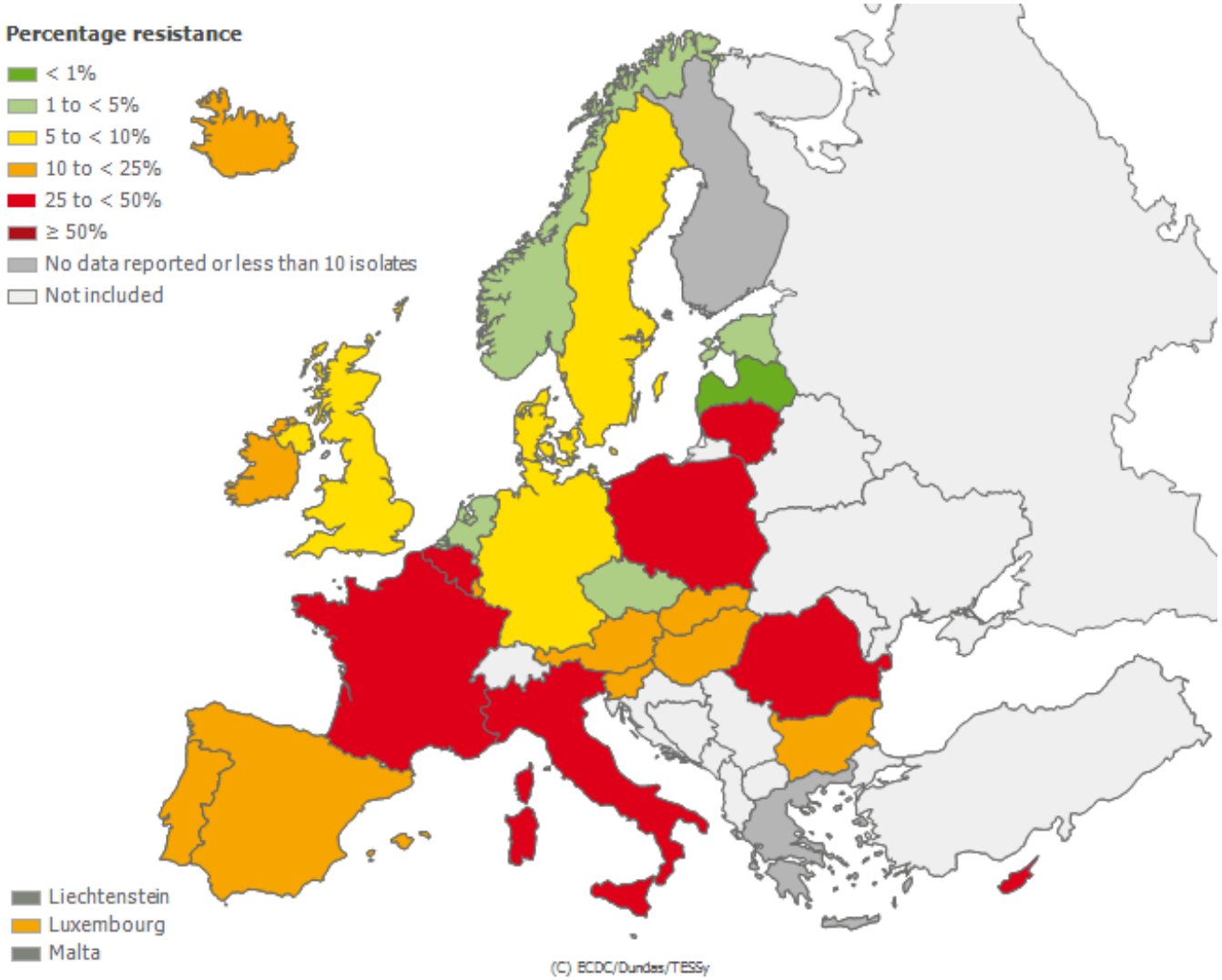
Belgian data:
Lismond et al. Int. J. Antimicrob Agents. 2012 Mar;39(3):208-16.

S. pneumoniae: how to make antibiotic policy





S. pneumoniae: European surveys of resistance to macrolides

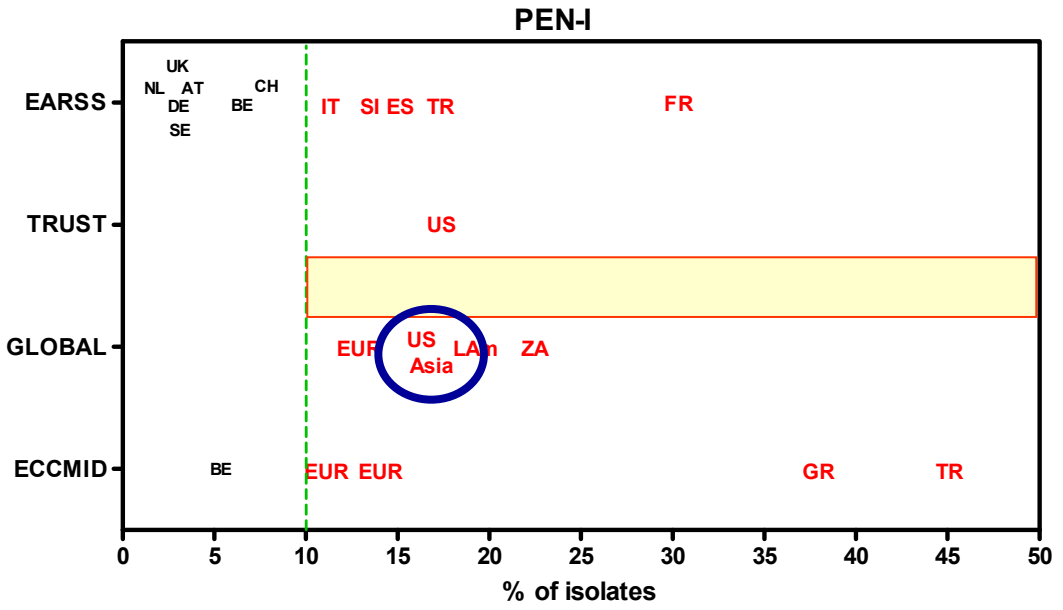


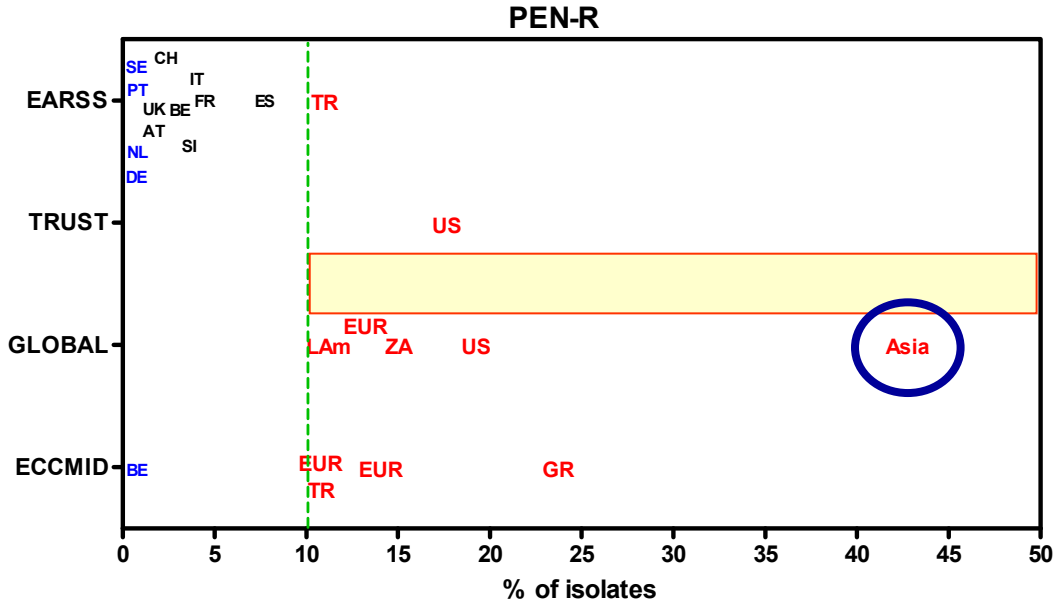
http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/maps_report.aspx

Resistance of *S. pneumoniae* International examples *

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

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





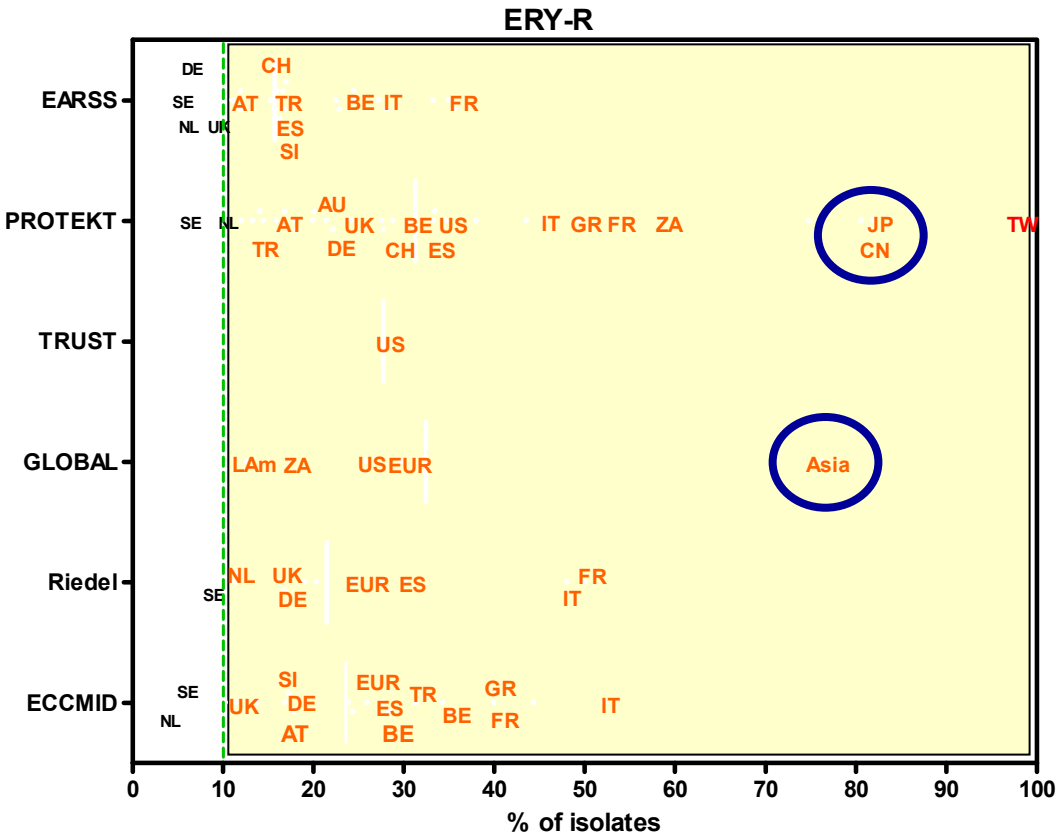
Carbonnelle *et al.*, in preparation

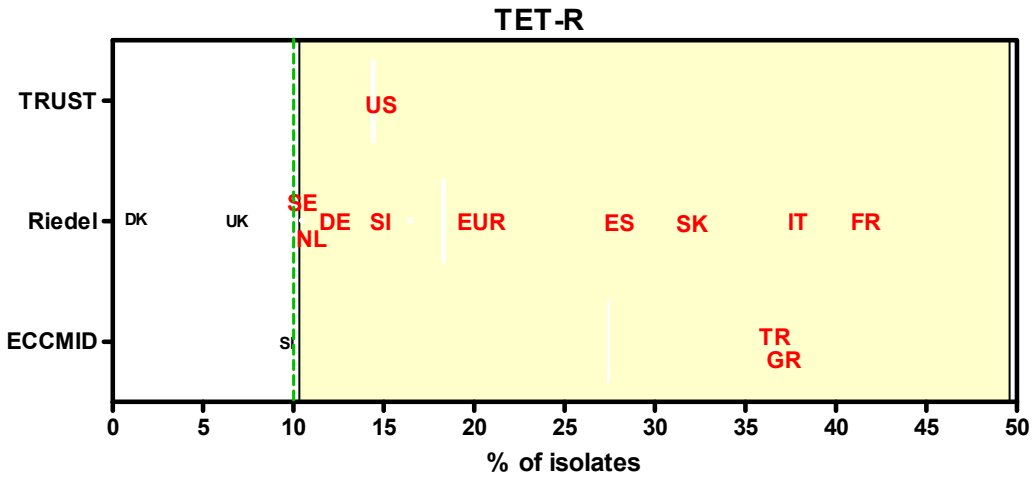
Resistance of *S. pneumoniae* International examples *

*analysis of resistance of 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

Carbonnelle *et al.*, in preparation





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Journals.ASM.org

A recent study of Asia

Changing Trends in Antimicrobial Resistance and Serotypes of *Streptococcus pneumoniae* Isolates in Asian Countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study

So Hyun Kim,[a] Jae-Hoon Song,[a,b] Doo Ryeon Chung,[b] Visanu Thamlikitkul,[c] Yonghong Yang,[d] Hui Wang,[e*] Min Lu,[f] Thomas Man-kit So,[g] Po-Ren Hsueh,[h] Rohani M. Yasin,[i] Celia C. Carlos,[j] Hung Van Pham,[k] M. K. Lalitha,[l] Nobuyuki Shimono,[m] Jennifer Perera,[n] Atef M. Shibl,[o] Jin Yang Baek,[a] Cheol-In Kang,[b] Kwan Soo Ko,[a,p] and Kyong Ran Peck[b] on behalf of the ANSORP Study Group

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Antimicrobial resistance in *Streptococcus pneumoniae* remains a serious concern worldwide, particularly in Asian countries, despite the introduction of heptavalent pneumococcal conjugate vaccine (PCV7). The Asian Network for Surveillance of Resistant Pathogens (ANSORP) performed a prospective surveillance study of 2,184 *S. pneumoniae* isolates collected from patients with pneumococcal infections from 60 hospitals in 11 Asian countries from 2008 to 2009. Among nonmeningeal isolates, the prevalence rate of penicillin-nonsusceptible pneumococci (MIC, ≥4 μg/ml) was 4.6% and penicillin resistance (MIC, ≥8 μg/ml) was extremely rare (0.7%). Resistance to erythromycin was very prevalent in the region (72.7%); the highest rates were in China (96.4%), Taiwan (84.9%), and Vietnam (80.7%). Multidrug resistance (MDR) was observed in 59.3% of isolates from Asian countries. Major serotypes were 19F (23.5%), 23F (10.0%), 19A (8.2%), 14 (7.3%), and 6B (7.3%). Overall, 52.5% of isolates showed PCV7 serotypes, ranging from 16.1% in Philippines to 75.1% in Vietnam. Serotypes 19A (8.2%), 3 (6.2%), and 6A (4.2%) were the most prominent non-PCV7 serotypes in the Asian region. Among isolates with serotype 19A, 86.0% and 79.8% showed erythromycin resistance and MDR, respectively. The most remarkable findings about the epidemiology of *S. pneumoniae* in Asian countries after the introduction of PCV7 were the high prevalence of macrolide resistance and MDR and distinctive increases in serotype 19A.

So Hyun Kim et al. Antimicrob. Agents Chemother. 2012, 56(3):1418.

Resistance in Vietnam: 1. Community

Hoa *et al. BMC Infectious Diseases* 2010, **10**:85
http://www.biomedcentral.com/1471-2334/10/85

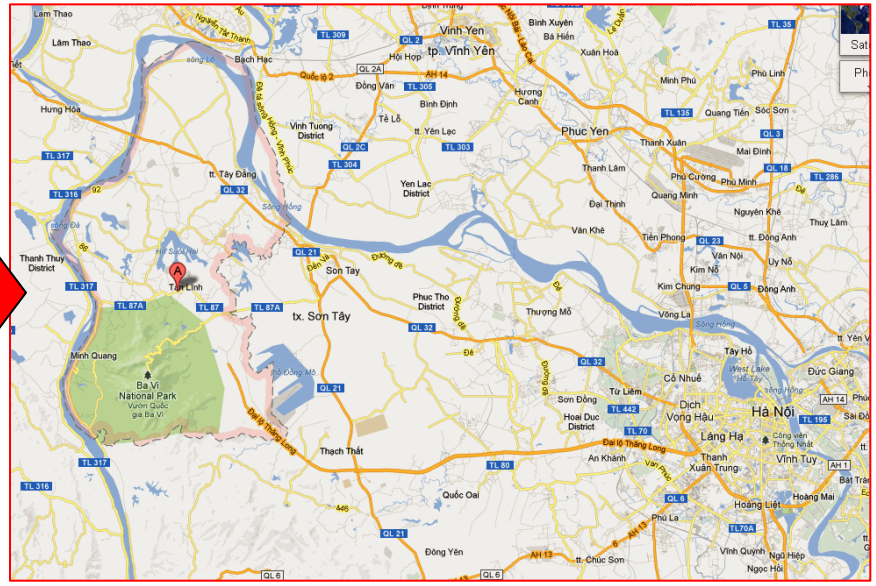
BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Decreased *Streptococcus pneumoniae* susceptibility to oral antibiotics among children in rural Vietnam: a community study

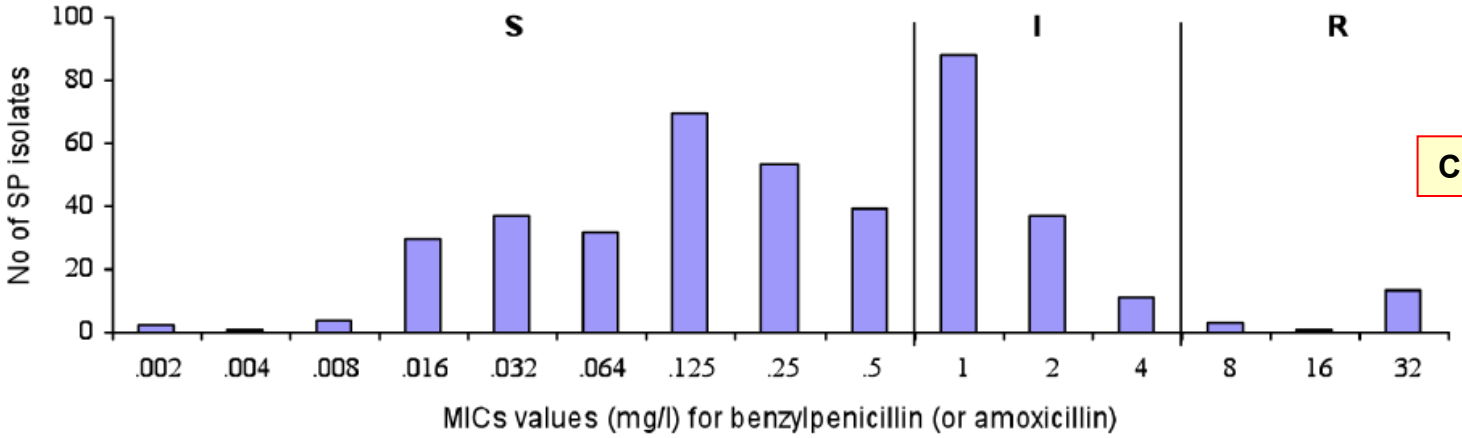
Nguyen Quynh Hoa[1,2*], Nguyen V Trung[3,4], Mattias Larsson[1], Bo Eriksson[5], Ho D Phuc[6], Nguyen TK Chuc[7], Cecilia Stalsby Lundborg[1]

Ba Vi District



Resistance for *S. pneumoniae* in Ba Vi District, Vietnam

421 isolates of *S. pneumoniae*.
95% (401/421) resistant to at least one clinically-used antibiotic



CLSI breakpoints

High level of resistance for
- co-trimoxazole (recommended by WHO !)
- tetracycline
- penicillin V
- erythromycin (70-78%; crossed resistance with other macrolides).

Resistance for *S. pneumoniae* in Ba Vi District, Vietnam

Resistance increases over time …

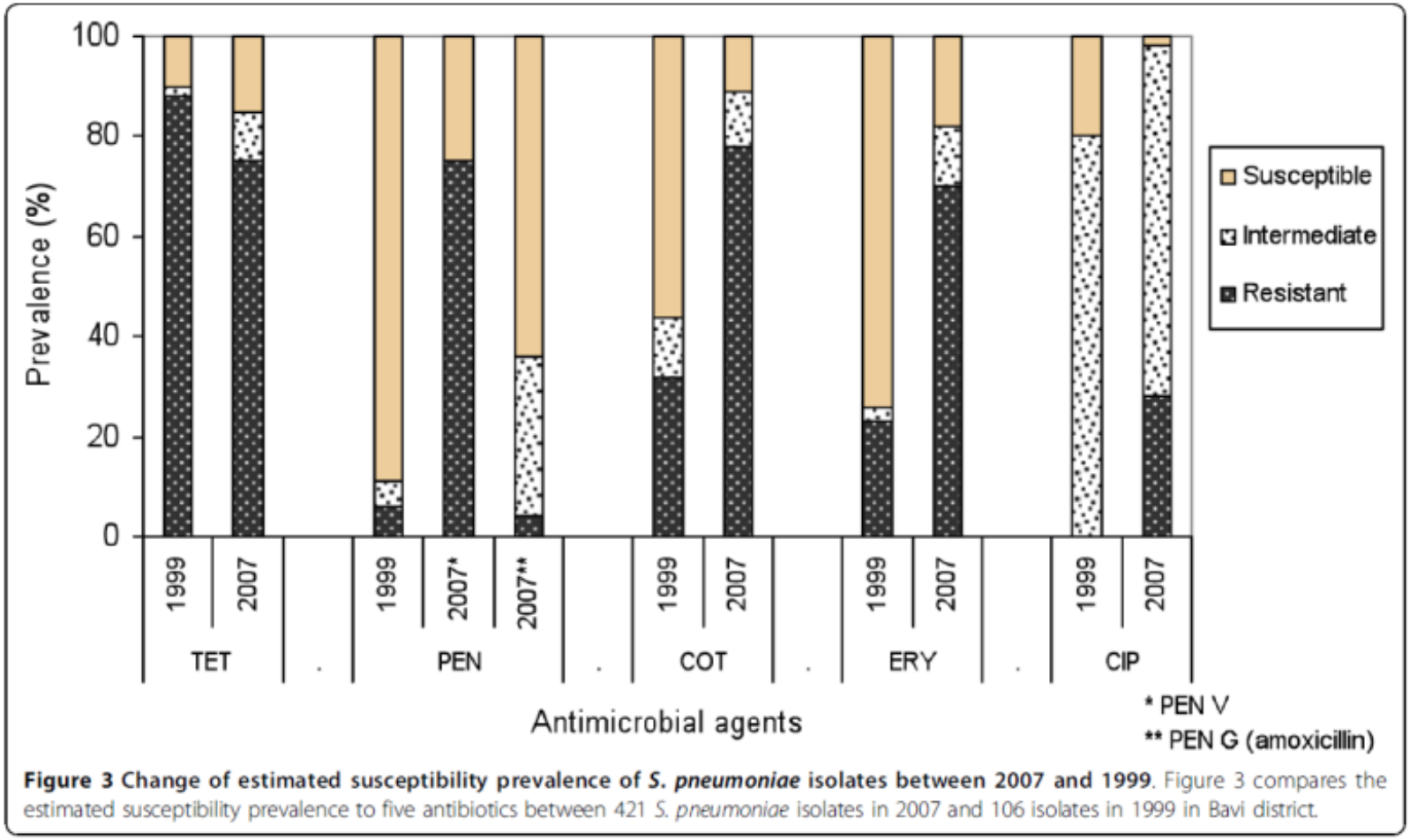


Figure 3 Change of estimated susceptibility prevalence of *S. pneumoniae* isolates between 2007 and 1999. Figure 3 compares the estimated susceptibility prevalence to five antibiotics between 421 *S. pneumoniae* isolates in 2007 and 106 isolates in 1999 in Bavi district.

Resistance and community antibiotic consumption in Vietnam

Conclusions: Resistance to commonly used antibiotics and multidrug-resistance of *S. pneumoniae* is markedly high. High dose of amoxicillin is the only oral antibiotic that can possibly be used when treatment is required for community-acquired pneumococcal infections. Most of children had used antibiotics unnecessarily during their most recent illness and in the 28-day period during the study. There is a serious lack of knowledge on appropriate antibiotic use among the HCPs as well as the caregivers. Antibiotics are often prescribed or dispensed for common colds.

Resistance in Vietnam: 2: Hospital

Pediatrics International (2008) **50**, 514–518 doi: 10.1111/j.1442-200X.2008.02616.x

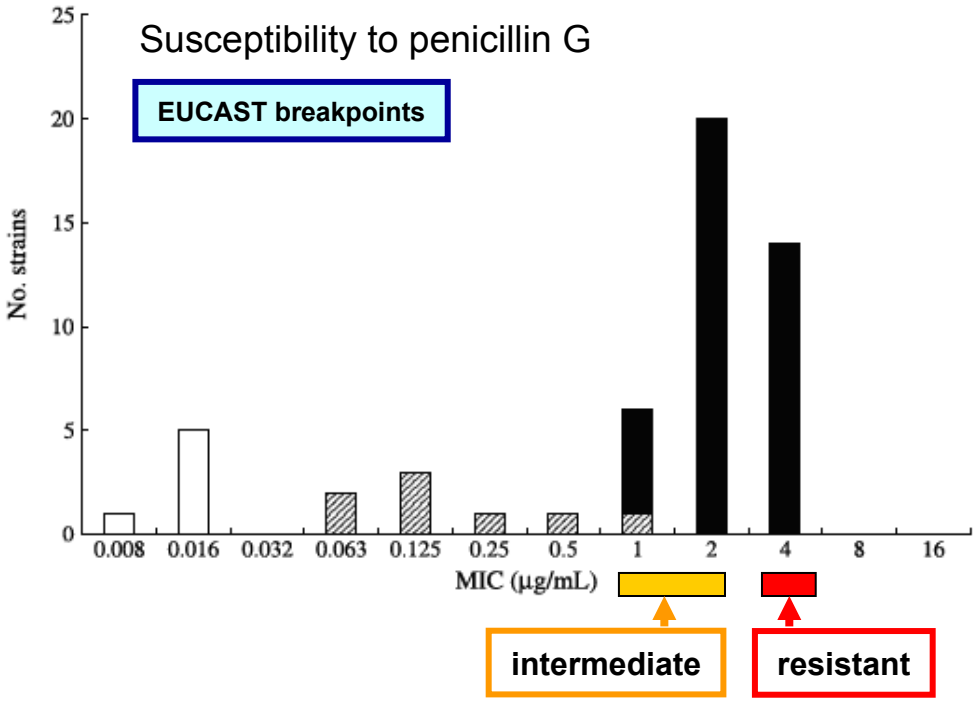
Original Article

Drug-resistant pneumococci in children with acute lower respiratory infections in Vietnam

Kiwao Watanabe,[1] Dang Duc Anh,[2] Phan Le Thanh Huong,[2] Nguyen Thu Nguyet,[3] Nguyen Thu Hien Anh,[2] Ngo Thi Thi,[3] Nguyen Tien Dung,[4] Doan Mai Phuong,[4] Olivia S. Rusizoka,[1] Tsuyoshi Nagatake,[1] Hiroshi Watanabe[1,†] and Kazunori Oishi[1,5]

Departments of [1]Internal Medicine and [5]Special Pathogen, International Research Center for Infectious Diseases, Institute of Microbial Diseases, Osaka University, Japan and [2]National Institute of Hygiene and Epidemiology, [3]Department of Laboratory, National Pediatric Hospital and [4]Department of Laboratory, Bach Mai Hospital, Hanoi, Vietnam

Resistance for *S. pneumoniae* at Bach Mai, Hanoi, Vietnam



Watanabe *et al*. Ped. Int. 2008; 50:514-518

Resistance for *S. pneumoniae* at Bach Mai, Hanoi, Vietnam

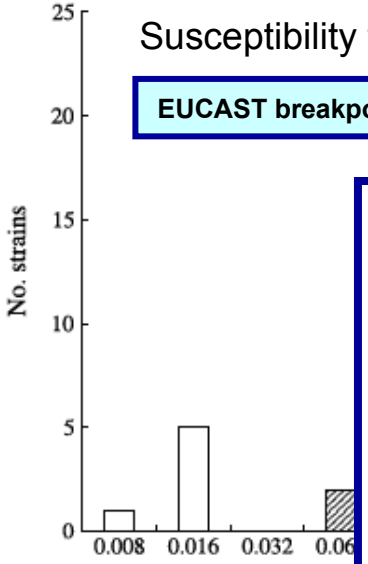


Table 2 Genotype of drug-resistant genes and MIC in 53 strains of *Streptococcus pneumoniae*

Genotype	*n* (%)	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
			Penicillin	
No mutation	6 (11.3)	0.01–0.02	0.02	0.02
pbp 2x + 2b	8 (15.1)	0.01–1.0	0.13	1
pbp 1a + 2x + 2b	39 (73.6)	1.0–4.0	2	4
			Erythromycin	
No mutation	7 (13.2)	0.01–0.06	0.03	0.06
MefA	4 (7.5)	0.5–4.0	1	4
ErmB	21 (39.6)	1.0–128	32	128
mefA + ermB	21 (39.6)	4.0–128	128	128

MIC, minimum inhibitory concentration.

Watanabe *et al*. Ped. Int. 2008; 50:514-518

Very recent Vietnamese data for respiratory tract infections in an hospital *

S. pneumoniae (n=44)						
Antibiotic	**no. tested**	**R (%)**	**I (%)**	**S (%)**	**MIC_{50}**	**MIC_{90}**
Erythromycin	38	**92.1**	2.6	5.3		
Chloramphenicol	34	**17.6**	0	82.4		
Clindamycin	38	**86.8**	0	13.2		
Vancomycin	37	0	0	100		
Cotrimoxazole	37	**94.6**	2.7	2.7		
Penicillin	43	**23.3**	**58.1**	18.6	0.38	1.5

CLSI breakpoints

* Bach Mai hospital, Hanoi (Jan-May 2013)

Resistance in a less severe indication: Maxillary rhinosinusitis

KHẢO SÁT VI TRÙNG VÀ KHÁNG SINH ĐỒ TRONG VIÊM XOANG HÀM MẠN TÍNH TẠI BỆNH VIỆN TAI MŨI HỌNG TP.HCM TỪ 12/2007-7/2008

Nguyễn Anh Tuấn*, Nguyễn Thị Ngọc Dung*, Phạm Hùng Vân*

***Kết quả**:*

VTHK thường gặp là Streptococci, Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis.

VTKK thường gặp là Propionibacterium acnes, Peptostreptococcus và trực khuẩn Gram (-).

Đối với VTHK, một số kháng sinh còn nhạy cảm tốt như Ciprofloxacin (77%), Levofloxacin (91%), Amoxicilline- clavulanic acid (87%).

Đối với VTKK, tất cả các kháng sinh trong kháng sinh đồ đều bị đề kháng cao (47-82%).

***Kết luận**: trong VXHMT tỉ lệ kháng sinh bị đề kháng tăng theo thời gian. Cần làm kháng sinh đồ để hạn chế sự đề kháng của kháng sinh.*

VTHK: vi trùng hiếu khí (aerobic bacteria)

VTKK: vi trùng kị khí (anaerobic bacteria)

VXHMT: viêm xoang hàm mãn tính (chronic maxillary rhinosinusitis)

Tạp chí Y học thành phố Hồ Chí Minh, năm 2009, tập 13, số 1, trang 201
Ho Chi Minh City Journal of Medicine, 2009, volume 13, Nr 1, page 201

The message: make and use surveys

- Countries (and Regions) should know THEIR resistance patterns!

The problem with the breakpoints

The impact of the change in CLSI breakpoints for *S. pneumoniae* and penicillin: an example from Latin America

Table 1 – Penicillin-resistance rates according to the 2007 CLSI and 2008 CLSI standards in pneumococcal strains collected from children hospitalized with pneumonia (1999 to 2008)

Resistance	n*	%	n†	%
Intermediate	22	22	1	1
Full	11	11	0	0
Total‡	33	33	1	1

CLSI = Clinical and Laboratory Standards Institute.
* According to the 2007 CLSI standard.
† According to the CLSI 2008 standard.
‡ Total of 100 strains analyzed.

No more resistance !

2007: S: ≤ 0.06, I: 0.12 to 1, R > 2 µg/mL
2008: S: ≤ 2 I: 4 to 8, R ≥ 8 µg:mL

In constrast to CLSI, EUCAST has always set breakpoints at **S ≤ 0.5 and R > 2**

Wolkers PC, et al. J Pediatr (Rio J) 2009;85(5):421-5.

CLSI (American) vs. EUCAST (American) breakpoints

CLSI breakpoints (Unites States)

- have long been notorious for being too high (too optimistic)
- are no longer official (hence the change of name from NCCLS (National Committee for Clinical Laboratory Standards) to CLSI (Clinical Laboratory Standard Institute)
- have a non-fully transparent setting system (highly influenced by Industry) and, therefore, often set too high (too optimistic)

EUCAST breakpoints (Europe)

- are totally independent from Industry (financed by the EU)
- are strongly based on both PK/PD and clinical data
- tend to be much lower (more severe) than CLSI breakpoints but probably more realistic

See more details about EUCAST at http://www.eucast.org

Conclusions

- Resistance to antibiotics is a widespread problem and intrinsic to the use of antibiotics
- The only real solution would be to NOT use antibiotics or to use them much less
  (there is compelling evidence that increase in antibiotic use increases the percentage of resistant strains)
- This is why alternative method of controlling bacteria are badly needed
  - either by blocking their multiplication right from the beginning (vaccinations, e.g.)
  - or by making them innocuous (anti-virulence strategies)

Supplement

Respiratory tract isolates in China – Taiwan – Indonesia - Singapore

International Journal of Antimicrobial Agents 38 (2011) 376–383

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Antimicrobial susceptibility of bacterial pathogens associated with community-acquired respiratory tract infections in Asia: report from the Community-Acquired Respiratory Tract Infection Pathogen Surveillance (CARTIPS) study, 2009–2010

Hui Wang[a,b], Minjun Chen[a,*], Yingchun Xu[a], Hongli Sun[a], Qiwen Yang[a], Yunjian Hu[c], Bin Cao[d], Yunzhuo Chu[e], Yong Liu[f], Rong Zhang[g], Yunsong Yu[h], Ziyong Sun[i], Chao Zhuo[j], Yuxing Ni[k], Bijie Hu[l], Thean Yen Tan[m], Po-Ren Hsueh[n,**], Jen-Hsien Wang[o], Wen-Chien Ko[p], Yen-Hsu Chen[q], Hendro Wahjono[r]

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[o] Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan
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[r] Department of Clinical Microbiology, Faculty of Medicine, Diponegoro University, Dr Kariadi Hospital, Semarang, Indonesia

RTI isolates (C-T-I-S): origin

2.1. Participating centres

A total of 17 centres in Asian countries took part in this study, including: Peking Union Medical College Hospital (Beijing, China); Beijing Hospital of the Ministry of Health (Beijing, China); Beijing Chao-Yang Hospital, Capital Medical University (Beijing, China); The First Hospital of China Medical University (Shenyang, China); The Second Hospital of China Medical University (Shenyang, China); The Second Affiliated Hospital of Medical School of Zhejiang University (Hangzhou, China); The First Affiliated Hospital of Medical School of Zhejiang University (Hangzhou, China); Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology (Wuhan, China); Guangzhou Institute of Respiratory Disease (Guangzhou, China); Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China); Zhongshan Hospital, Fudan University (Shanghai, China); National Taiwan University Hospital (Taiwan); China Medical University Hospital (Taiwan); National Cheng Kung University Hospital (Taiwan); Kaohsiung Medical University Hospital (Taiwan); Diponegoro University/Dr Kariadi Hospital (Indonesia); and Changi General Hospital (Singapore).

RTI isolates (C-T-I-S): *S. pneumoniae*

In vitro activity against 706 isolates of Streptococcus pneumoniae, based on activity against penicillin-susceptible (PSSP), penicillin-intermediate (PISP) and penicillin-resistant (PRSP).isolates

Antibiotic	Mainland China ($n = 420$)			
	No.	%R	MIC_{50} (mg/L)	MIC_{90} (mg/L)
AMC				
PSSP	203	0	0.032	0.032
PISP	98	0	0.5	2
PRSP	103	21.4	4	8
Cefuroxime (parenteral)				
PSSP		0.5	0.125	0.125
PISP		73.5	4	8
PRSP		100	8	32
Cefuroxime (oral)				
PSSP		0	0.125	0.125
PISP		53	4	8
PRSP		100	8	32
Cefaclor				
PSSP		0.5	0.5	1
PISP		86.7	16	128
PRSP		100	128	128
Ceftriaxone				
PSSP		0.5	0.032	0.064
PISP		3.1	0.5	1
PRSP		37.9	2	4

RTI isolates: *Haemophilus influenzae and Moraxella catarrhalis*

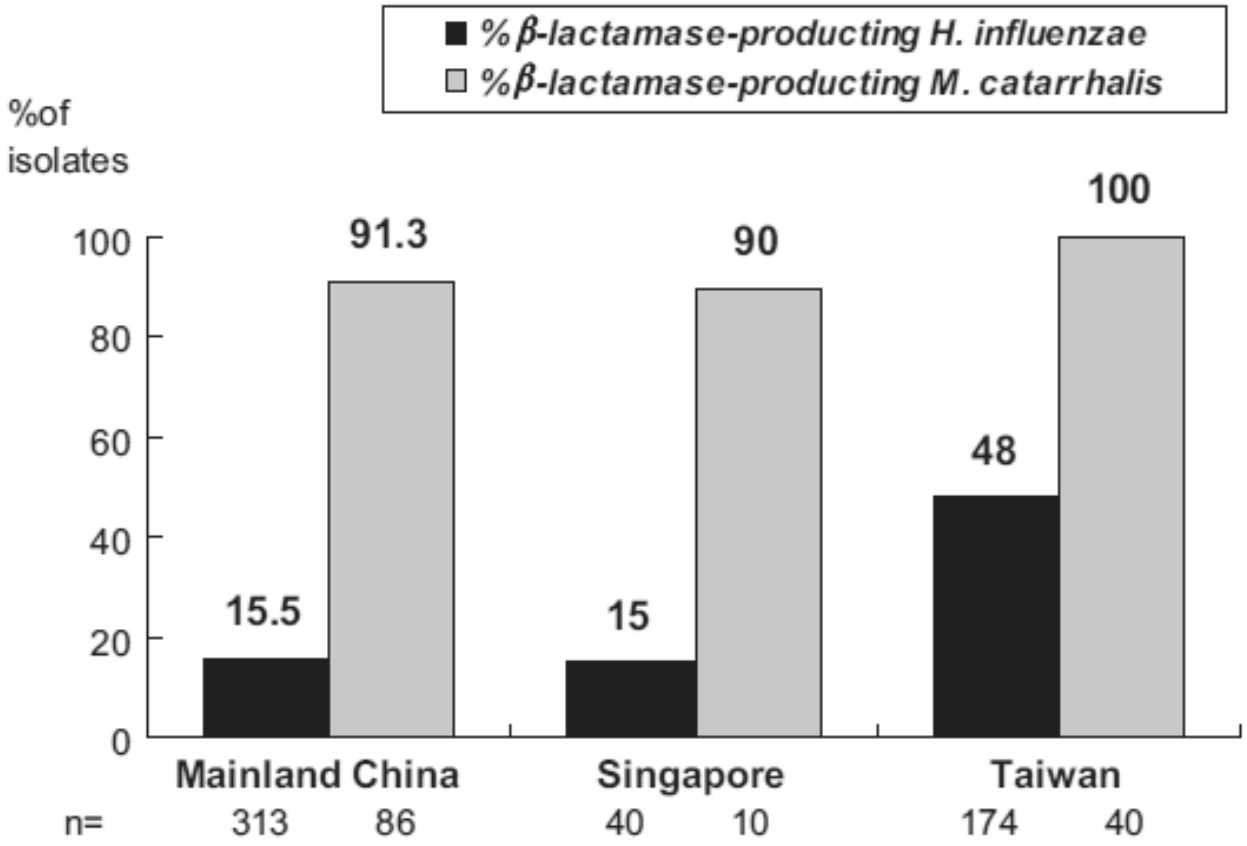

Fig. 2. Proportions of β-lactamase production amongst *Haemophilus influenzae* and *Moraxella catarrhalis* isolates from Asian countries.

P.aeruginosa

- Li M, Pan P, Hu C. [Pathogen distribution and antibiotic resistance for hospital aquired pneumonia in respiratory medicine intensive care unit]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2013 Mar;38(3):251-7.
  - pathogen distribution and antibiotic resistance of pathogens isolated from in-patients with hospital acquired pneumonia (HAP) in the Department of Respiratory Medicine Intensive Care Unit (RICU) of Xiangya Hospital in 2005 and in 2011,
  - infection rate of Pseudomonas aeruginosa reduced from 20.42% in 2005 to 15.60% in 2011
  - The resistance rate of *Pseudomonas aeruginosa* to levofloxacin, cyclopropane, amicacin, gentamicin, meropenem, cematrixone, and piperacilintazobactam increased obviously (P<0.05).

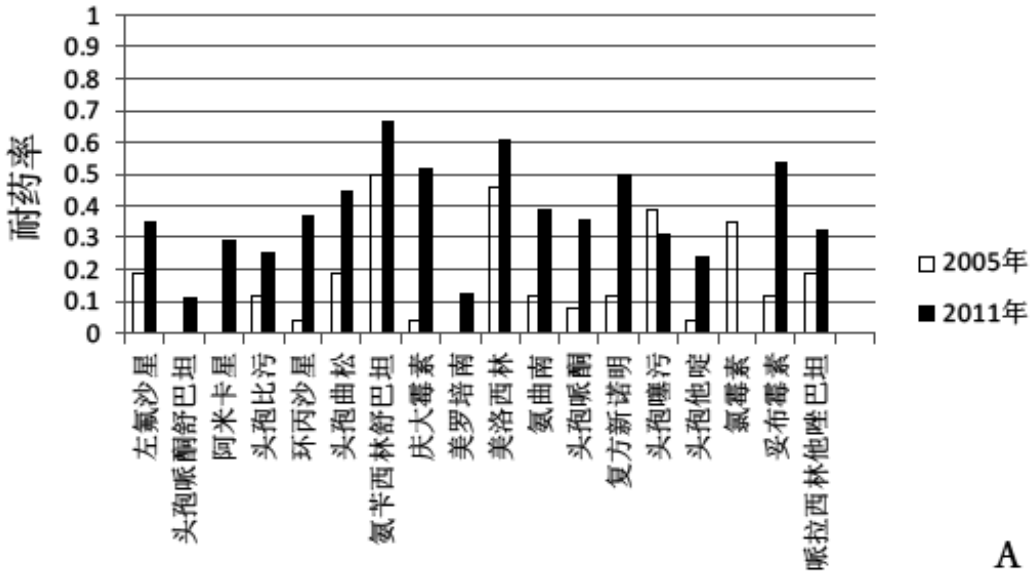

图2　两种主要革兰阴性杆菌2005年与2011年的耐药率比较。A：铜绿假单胞菌；B：鲍曼不动杆菌。

Figure 2 Drug resistance rate of 2 kinds of major Gram negative bacteria in 2005 and in 2011. A: *Pseudomonas aeruginosa;*