Pneumonia: not just a Gram-negative issue ?

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Vietnam Workshop
Practical approaches to antibiotic use for pneumonia
Taipei, Taiwan

With approval of the Belgian Common Ethical Health Platform – visa no. 16/V1/7383/078554

Which burden ?

- CAP:
  - A major acute cause of death (3rd to 7th);
  - Clear association between aging and pneumonia (“a friend of the elderly.”) [1]
  - Hospitalization rates for pneumonia have also increased significantly over the last 15 years [2]
  - High levels in long-term-care facilities [3]
    → “health care associated” pneumonia ?
  - Costly treatments of elderly patients because of the increased length of hospital [4]
  - Long term survival is often poor (half of elderly patients with community-acquired pneumonia died in the next year) [5]

[1] Osler W The Principles and Practice of Medicine. 3rd ed 1898 Appleton New York 109
[2] Fry *et al.* JAMA. 294:2712-2719 2005
[3] Marrie TJ. Infect Control Hosp Epidemiol. 23:159-164 2002
[4] Marston *et al.* Arch Intern Med. 157:1709-1718 1997
[5] Kaplan *et al.* Arch Intern Med. 163:317-323 2003

Contents of the presentation

- **The diseases and the enemies**
- **From enemies to antibiotics: which ones to use ?**
- **The fear for resistance**
- **Epidemiology**
- **Conclusions and Recommendations**

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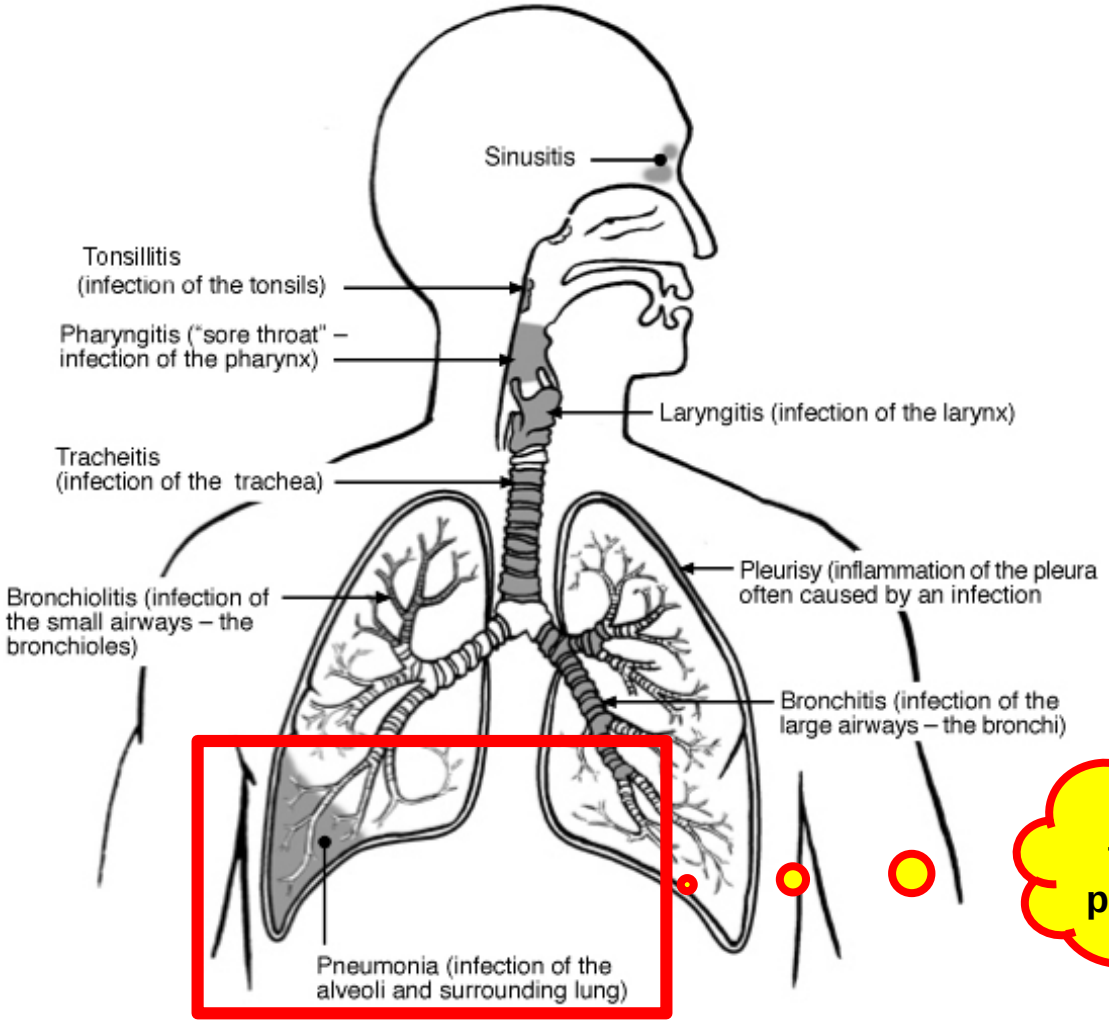
Respiratory tract infections: 1. the diseases



Infections of the respiratory tract

we will focus on pneumonia

Respiratory tract infections: 2. the enemies

Pneumonia in patients coming from the community: which type ?

- **community acquired (CAP)**
  - Children
  - Young adult patients with no risk factor
  - Elderly
  - Comorbidities and severity of disease
- **health care associated (HCAP)**
  - nursing homes or previous antibiotic treatments
  - 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

the most prevalent one

↗ in young adults

↗ in severe cases

↗ in severe cases and comorbidities

↗ in local environments (!!!)

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

Main pathogens in HCAP associated pneumonia

All of the above plus

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

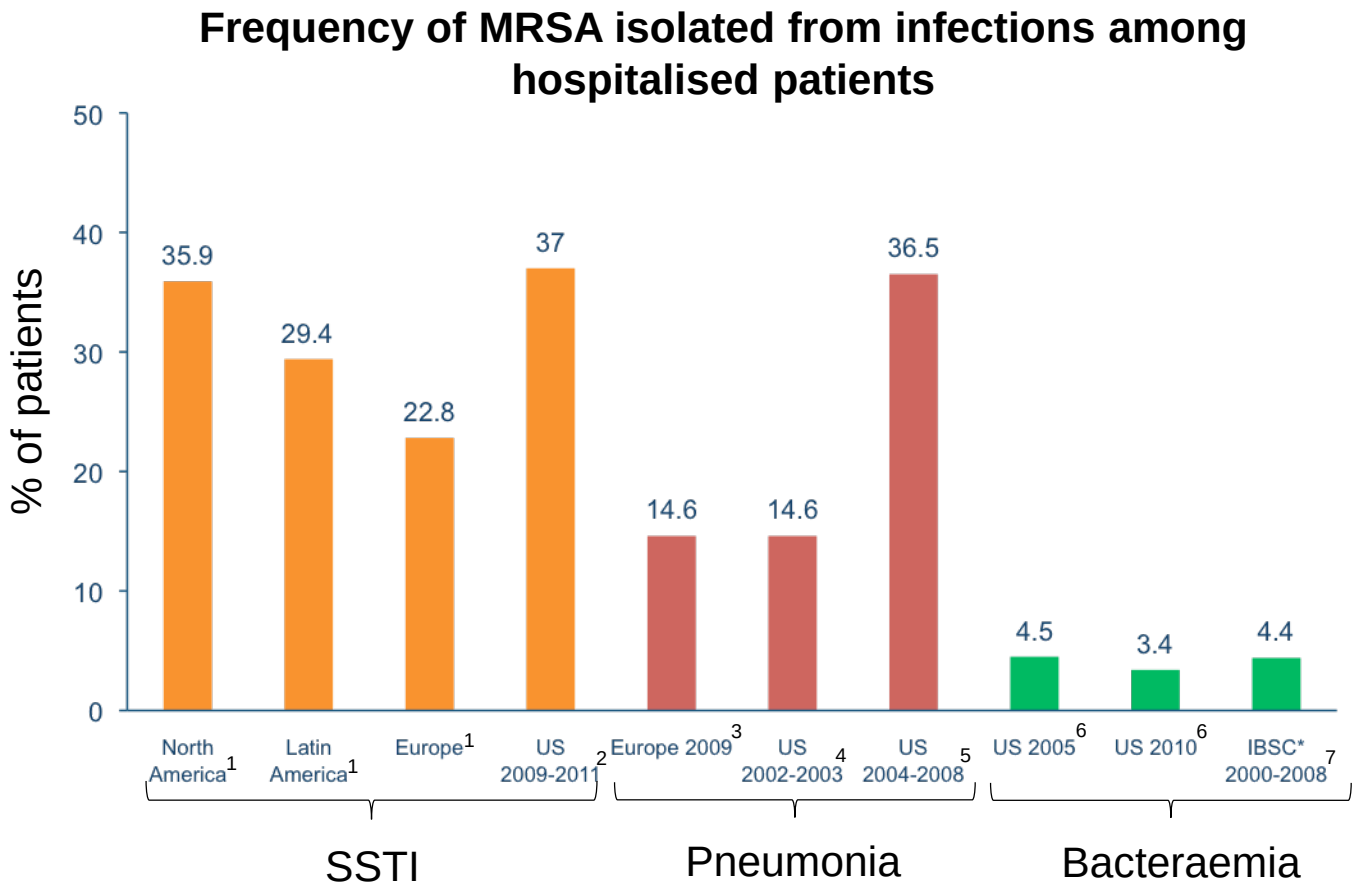
Donowithz G. Acute pneumonia: health-care assciated pneumonia In Priciples and Practie of Infectious Diseases, Mandell et al. eds, 7th Edition on line - chapter 64 (https://expertconsult.inkling.com/read/principles-practice-infectious-diseases-mandell-7th/chapter-64/pneumonia-syndromes#87a18782a8ba440c91948961322e0397)

CAP and HCAP : a comparison of etiologies

Pathogen, n (%)	CAP (n=208)	HCAP (n=431)	P value
MRSA	**25 (12.0)**	**132 (30.6)**	<0.001
S. pneumoniae	**85 (40.9)**	45 (10.4)	<0.001
P. aeruginosa	10 (4.8)	**110 (25.5)**	<0.001
MSSA	**28 (13.5)**	**60 (13.9)**	0.874
Haemophilus species	**36 (17.3)**	18 (4.2)	<0.001
Other nonfermenting Gram-negative rods	4 (1.9)	43 (10.0)	<0.001
Other Enterobacteriaceae	5 (2.4)	39 (9.0)	0.002
Klebsiella species	7 (3.4)	28 (6.5)	0.103
E. coli	12 (5.8)	18 (4.2)	0.372
Legionella species	7 (3.4)	1 (0.2)	0.017

Micek *et al. Antimicrob Agents Chemother.* 2007; 51:3568-73.

MRSA is a Frequent Cause of Hospital-acquired Infections in many parts of the world



SSTI = skin and skin-structure infection
IBSC = International Bacteremia Surveillance Collaborative (Finland, Australia, Canada, Denmark and Sweden)

1. Moet GJ, et al. Diagn Microbiol Infect Dis 2007;57:7–13; 2. Ray GT, et al. BMC Infect Dis. 2013;13(1):252; 3. Koulenti D, et al. Crit Care Med 2009;37:2360-2368; 4. Kollef MH, et al. Chest 2005;128:3854-3862; 5. Jones RN, Clin Infect Dis 2010;51 Suppl 1:S81–7; 6. Landrum ML, et al. JAMA 2012;308:50-9; 7. Laupland M, et al. Clin Microbiol Infect 2013;19:465–471.

But also in Asia: spread of CA-MRSA ?

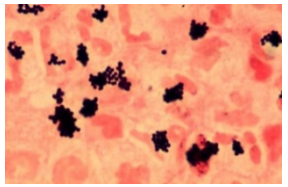
J Antimicrob Chemother 2011; **66**: 1061–1069
doi:10.1093/jac/dkr024 Advance Access publication 20 February 2011

Journal of Antimicrobial Chemotherapy

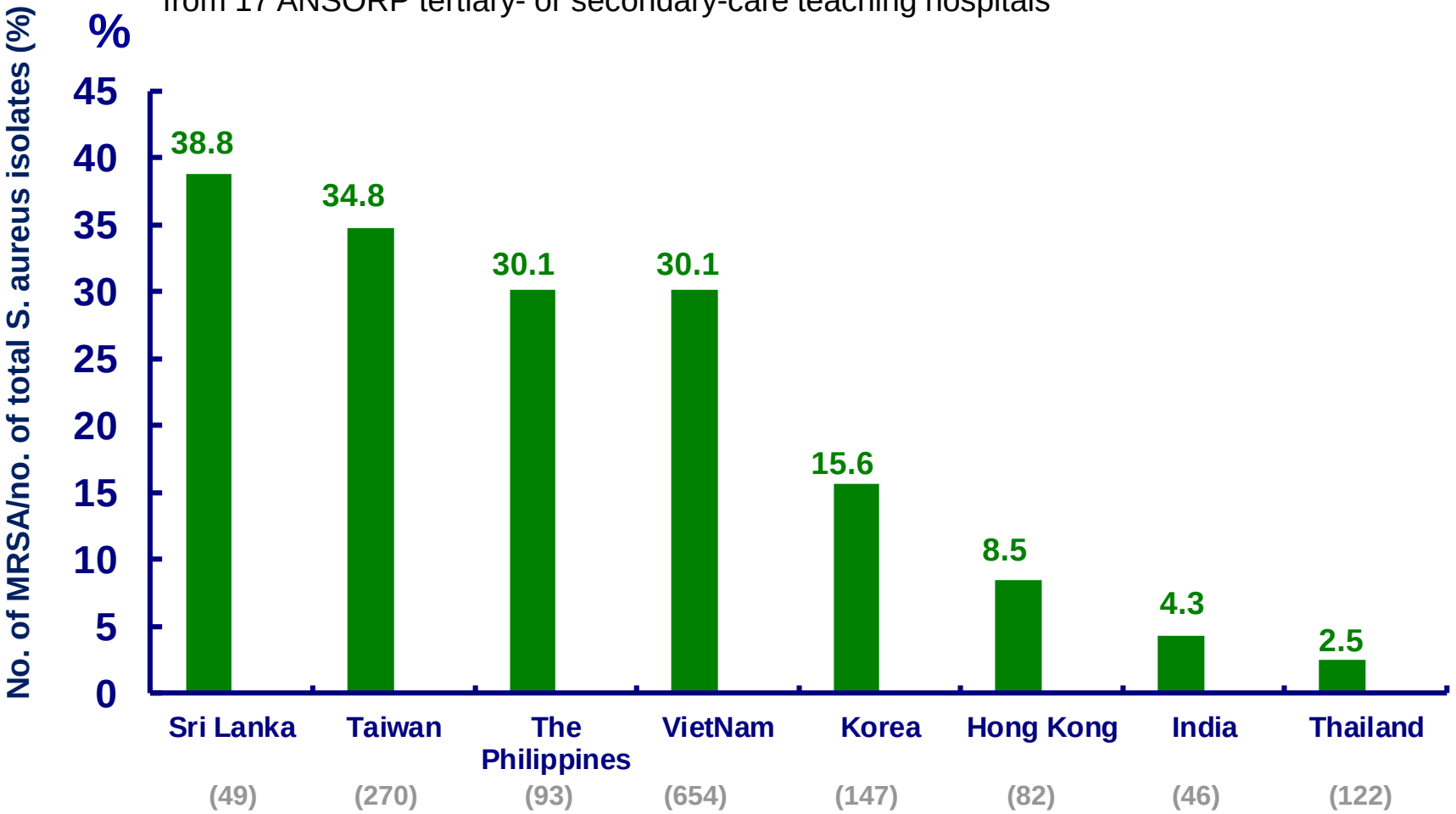
Spread of methicillin-resistant *Staphylococcus aureus* between the community and the hospitals in Asian countries: an ANSORP study

Jae-Hoon Song[1,2]*†, Po-Ren Hsueh[3]†, Doo Ryeon Chung[1], Kwan Soo Ko[2,4], Cheol-In Kang[1], Kyong Ran Peck[1], Joon-Sup Yeom[5], Shin-Woo Kim[6], Hyun-Ha Chang[6], Yeon-Sook Kim[7], Sook-In Jung[8], Jun Seong Son[9], Thomas Man-kit So[10], M. K. Lalitha[11], Yonghong Yang[12], Shao-Guang Huang[13], Hui Wang[14], Quan Lu[15], Celia C. Carlos[16], Jennifer A. Perera[17], Cheng-Hsun Chiu[18], Jien-Wei Liu[19], Anan Chongthaleong[20], Visanu Thamlikitkul[21] and Pham Hung Van[22] on behalf of the ANSORP Study Group‡

But also in Asia: spread of CA-MRSA ?

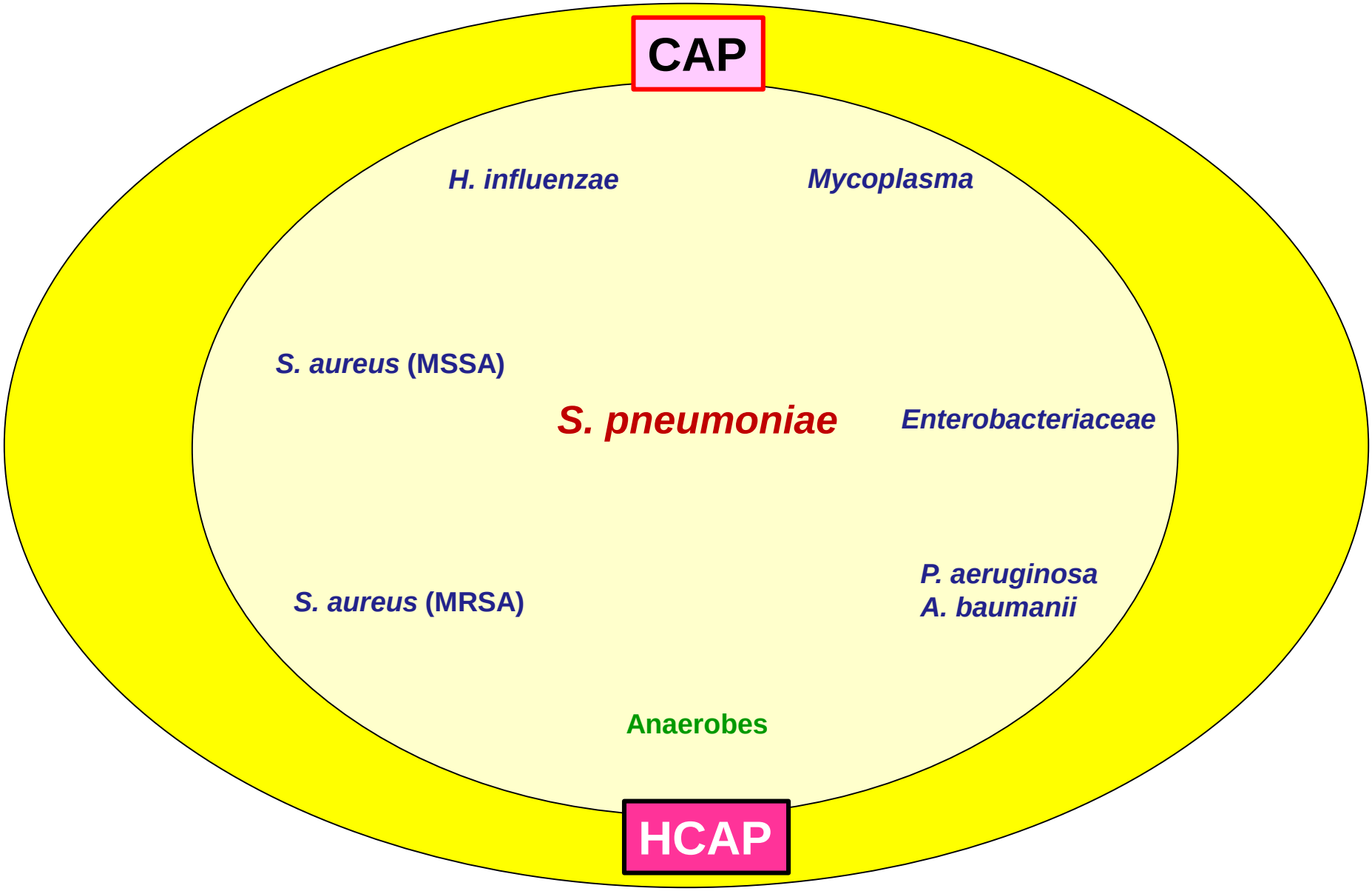


4117 isolates from patients with clinically demonstrated *S. aureus* infection from 17 ANSORP tertiary- or secondary-care teaching hospitals



Song *et al*. J Antimicrob Chemother. 2011;66:1061-9.

In a nutshell (for bacteria) …



Message(s)

- Talk to your microbiologist
- Invest MORE in microbiology
- Trust microbiology
- Use microbiological surveys data

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Avoid inappropriate treatments in HCAP …

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2007, p. 3568–3573 Vol. 51, No. 10
0066-4804/07/$08.00+0 doi:10.1128/AAC.00851-07

Health Care-Associated Pneumonia and Community-Acquired Pneumonia: a Single-Center Experience[▽]

Scott T. Micek,[1] Katherine E. Kollef,[2] Richard M. Reichley,[3] Nareg Roubinian,[2] and Marin H. Kollef[2]*

Department of Pharmacy, Barnes-Jewish Hospital, St. Louis, Missouri[1]; Pulmonary and Critical Care Division, Washington University School of Medicine, St. Louis, Missouri[2]; and BJC Health Care, Center for Health Care Quality and Effectiveness, St. Louis, Missouri[3]

Received 29 June 2007/Returned for modification 24 July 2007/Accepted 31 July 2007

Avoid inappropriate treatments …

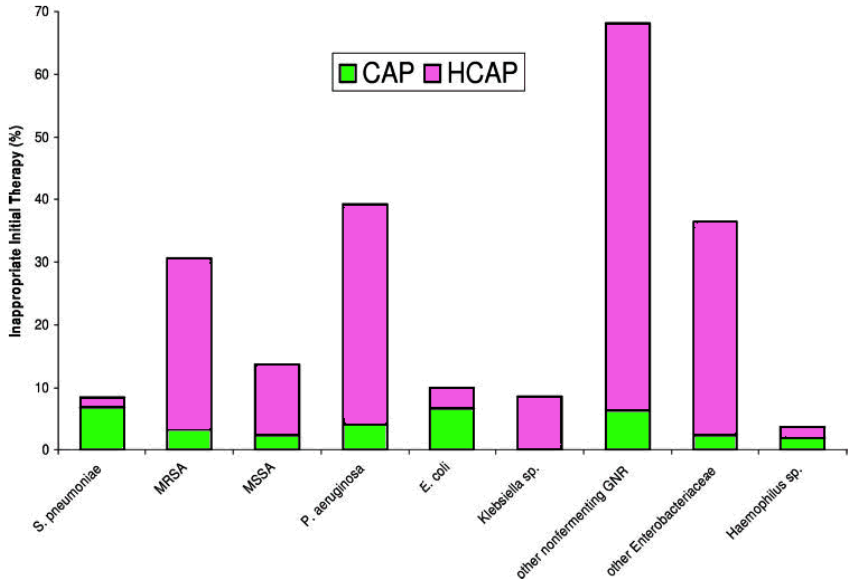

FIG. 1. Rates of inappropriate antimicrobial treatment in patients according to pathogen distribution.

inappropriate therapies

mortalities

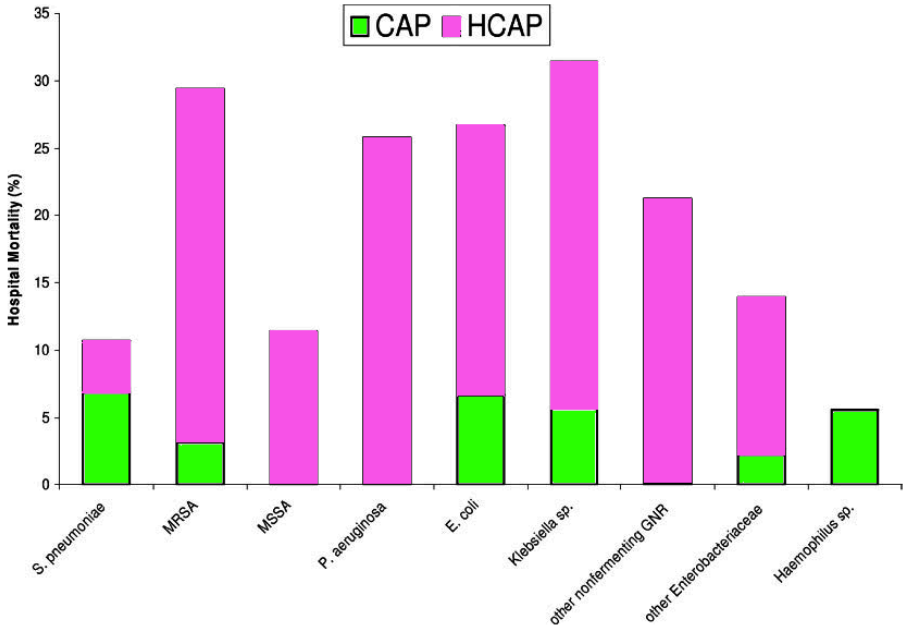

FIG. 2. Rates of hospital mortality according to pathogen distribution. GNR, gram-negative rods.

Micek *et al. Antimicrob Agents Chemother.* 2007; 51:3568-73.

A choice of antibiotics based on EUCAST…

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

- Organization
- EUCAST News
- Clinical breakpoints
- Expert rules and intrinsic resistance
- Resistance mechanisms
- Guidance documents
- MIC distributions and ECOFFs

The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST deals with **breakpoints** and technical aspects of phenotypic in vitro **antimicrobial susceptibility testing** and functions as the breakpoint committee of EMA and ECDC.

A choice of antibiotics based on EUCAST…

EUCAST
EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
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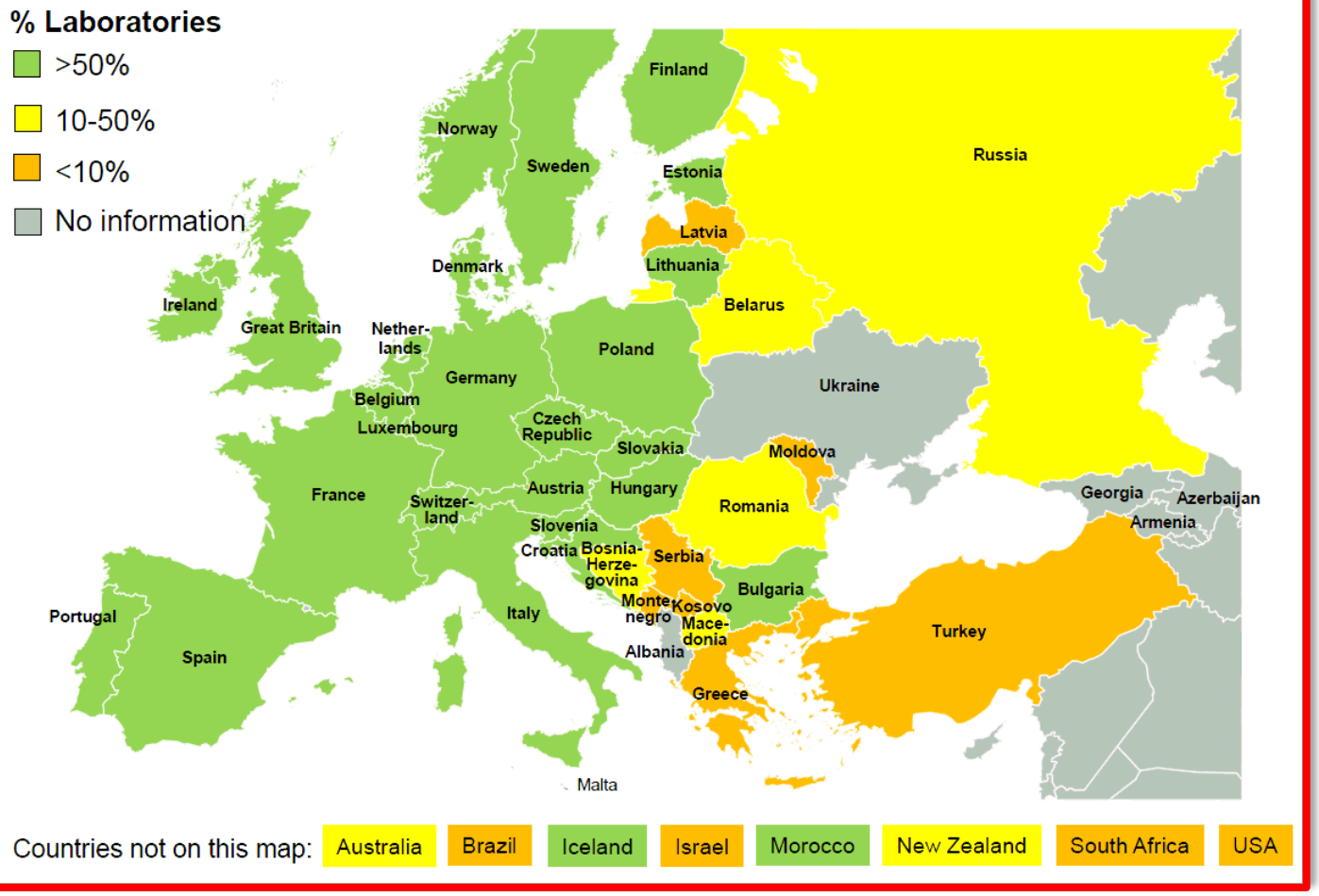
Implementation of EUCAST breakpoints, April 2015



Here are some proposals…[a]

S. pneumoniae [c]	clinical breakpoint (mg/L) [b]	
	susceptible	resistant
β-lactams		
amoxicillin	**≤ 0.5**	**> 2**
ceftriaxone	**≤ 0.5**	**> 2**
ertapenem	**≤ 0.5**	**> 0.5**
meropenem	**≤ 2**	**> 2**
macrolides		
azithromycin	**≤ 0.25**	**> 0.5**
clarithromycin	**≤ 0.25**	**> 0.5**
fluoroquinolones		
levofloxacin [d]	**≤ 2**	**> 2**
moxifloxacin	**≤ 0.5**	**> 1**
glycopeptides		
vancomycin	**≤ 2**	**> 2**
tetracyclines		
doxycycline	**≤ 1**	**> 2**

[a] more details and proposals on http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf
[b] susceptible: high likelihood of clinical success; resistant: high likelihood of clinical failure
[c] non-meningitis indication
[d] high dose (2 X 500 mg/day)

Here are some proposals…[a]

MRSA	clinical breakpoint (mg/L) [b]	
	susceptible	resistant
β-lactams		
ceftaroline	**≤ 1**	**> 1**
macrolides		
clarithromycin	**≤ 1**	**> 2**
fluoroquinolones		
moxifloxacin [c]	**≤ 0.5**	**> 1**
glycopeptides		
vancomycin	**≤ 2**	**> 2**
tetracyclines		
doxycycline	**≤ 1**	**> 2**
tigecycline	**≤ 0.5**	**> 0.5**
Oxazolidinones		
linezolid	**≤ 4**	**> 4**
tedizolid	**≤ 0.5**	**> 0.5**
Trimethoprim/Sulfamethoxazole	**≤ 2**	**> 4**

[a] more details and proposals on http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf
[b] susceptible: high likelihood of clinical success; resistant: high likelihood of clinical failure
[c] moxifloxacin has no indication for MRSA but some strains show low MICs (testing is essential)

Here are some proposals…[a]

Enterobacteriaceae	clinical breakpoint (mg/L) [b]	
	susceptible	resistant
β-lactams		
amoxicillin/clavulanic acid	**≤ 8**	**> 8**
piperacillin/tazobactam	**≤ 8**	**> 16**
ceftazidime	**≤ 1**	**> 4**
ceftriaxone	**≤ 1**	**> 2**
ertapenem	**≤ 0.5**	**> 1**
meropenem	**≤ 2**	**> 8**
fluoroquinolones		
ciprofloxacin	**≤ 0.5**	**> 1**
moxifloxacin	**≤ 0.5**	**> 1**
aminoglycosides		
gentamicin	**≤ 1**	**> 4**
amikacin	**≤ 4**	**> 16**
polymyxins		
colistin	**≤ 2**	**> 2**

[a] more details and proposals on http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf
[b] susceptible: high likelihood of clinical success; resistant: high likelihood of clinical failure

Here are some proposals…[a]

Pseudomonas aeruginosa	clinical breakpoint (mg/L) [b]	
	susceptible	resistant
β-lactams		
piperacillin/tazobactam	**≤ 16**	**> 16**
ceftazidime	**≤ 8**	**> 8**
cefepime	**≤ 8**	**> 8**
meropenem	**≤ 2**	**> 8**
fluoroquinolones		
ciprofloxacin	**≤ 0.5**	**> 1**
levofloxacin	**≤ 1**	**> 2**
aminoglycosides		
gentamicin	**≤ 4**	**> 4**
amikacin	**≤ 8**	**>16**
polymyxins		
colistin	**≤ 4**	**> 4**

[a] more details and proposals on http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf
[b] susceptible: high likelihood of clinical success; resistant: high likelihood of clinical failure

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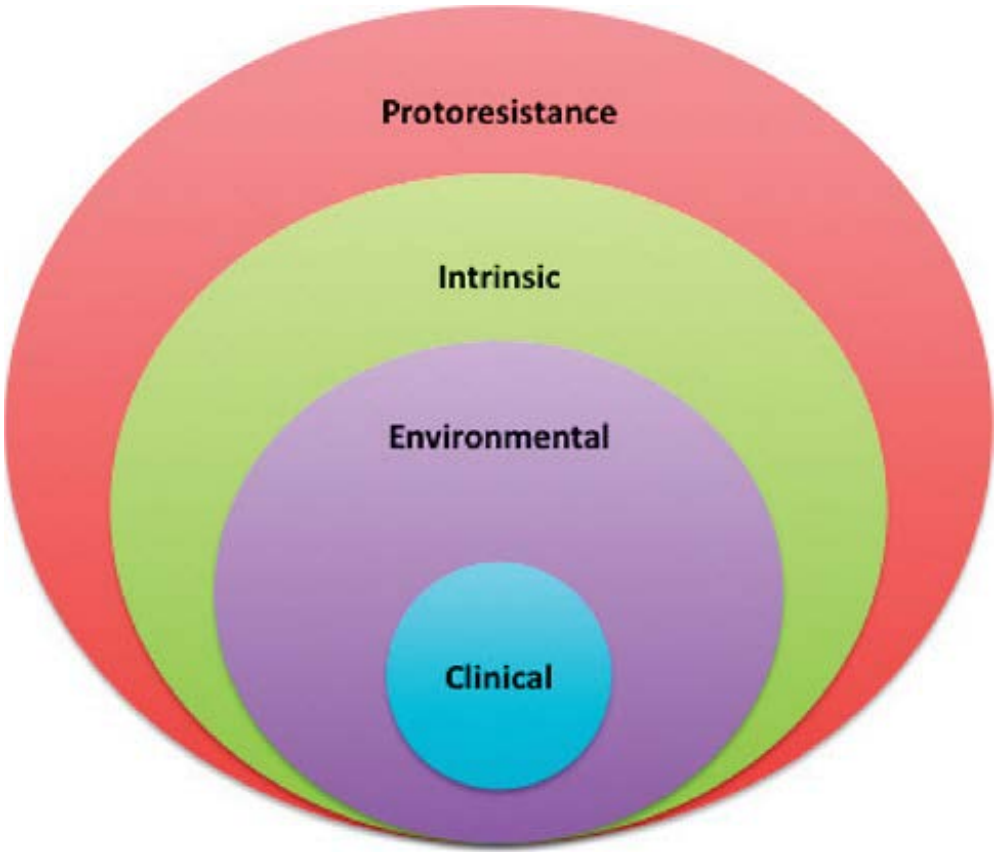
The resistome …

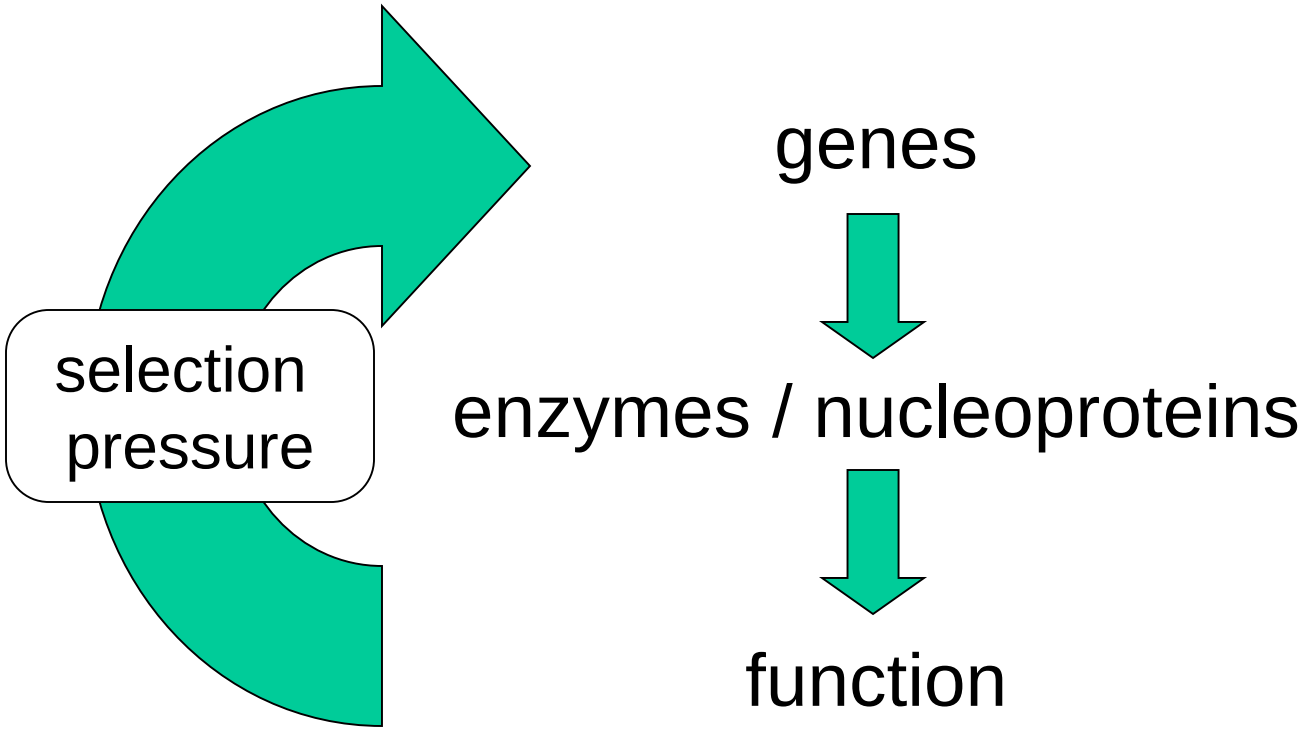


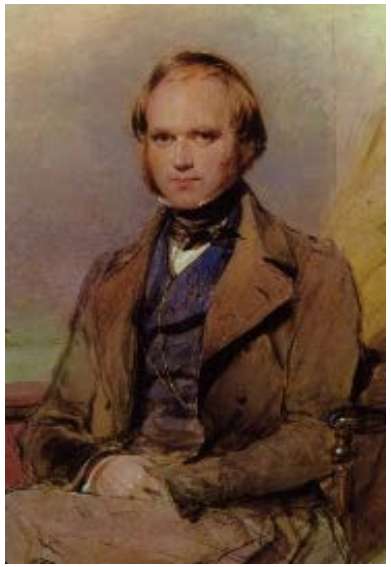
- all the genes and their products that contribute to antibiotic resistance
- highly redundant and interlocked system
- clinical resistance under represents the resistance capacity of bacteria
- existing biochemical mechanisms (protoresistome) serve as a deep reservoir of precursors that can be co-opted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

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

The selectome

A simple application of Darwin's principles ...



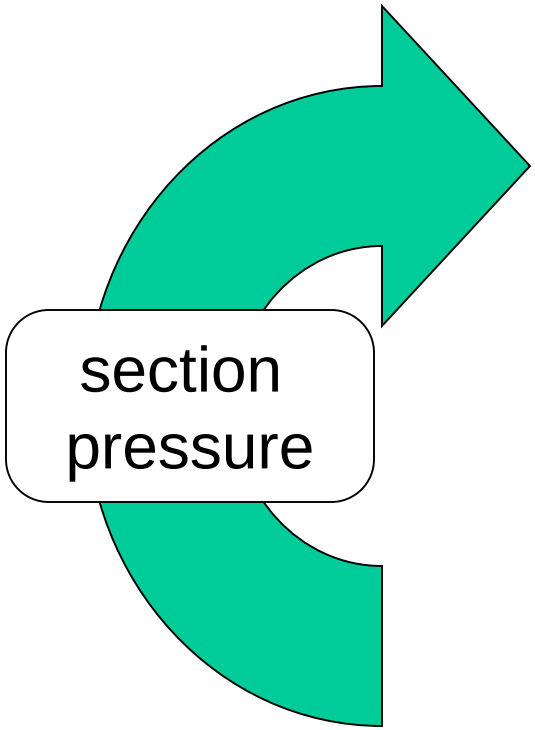


Detail of watercolor by
George Richmond, 1840.
Darwin Museum at Down House

How and why can you select so easily ?

A simple application of Darwin's principle…

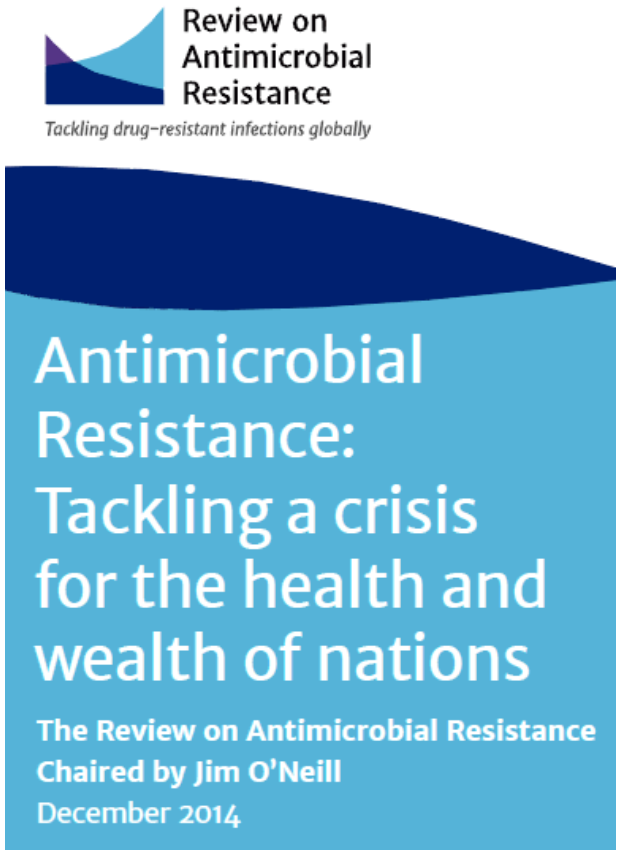
to a highly plastic material…



- 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

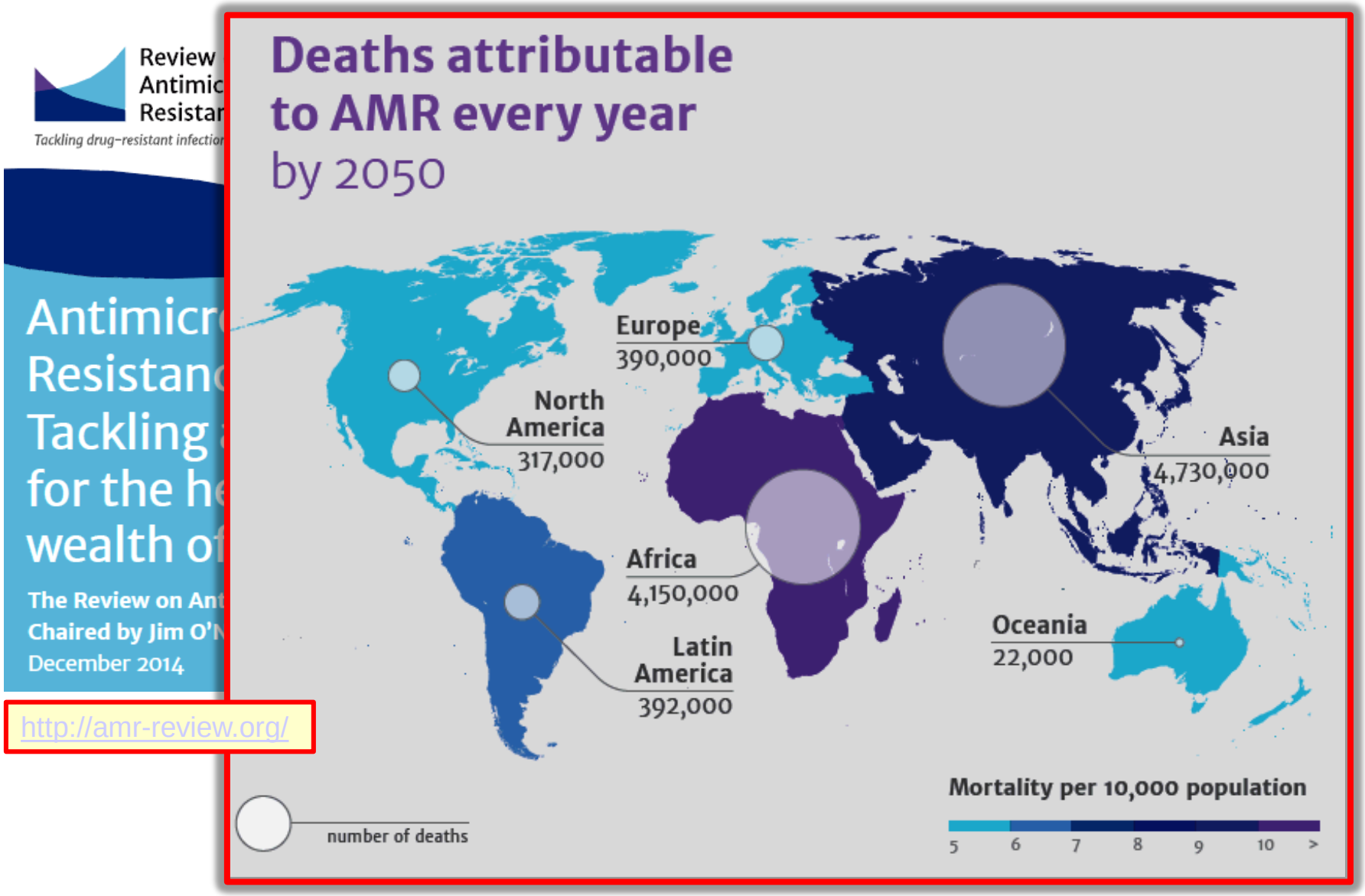
fast selection of the fittest !

What are the risks ?



http://amr-review.org/

What are the risks ?



AMR: antimicrobial resistance

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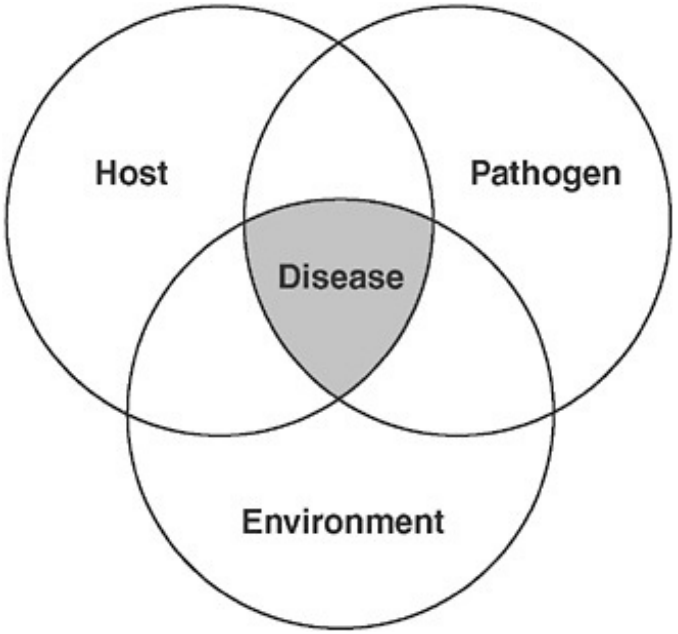
Epidemiology



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)

Resistance in Cambodia and neighboring countries

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PLOS | ONE

Etiologies and Resistance Profiles of Bacterial Community-Acquired Pneumonia in Cambodian and Neighboring Countries' Health Care Settings: A Systematic Review (1995 to 2012)

Sophie Goyet[1], Erika Vlieghe[2], Varun Kumar[3], Steven Newell[4], Catrin E. Moore[3,5,6], Rachel Bousfield[3,6], Heng C. Leang[7], Sokheng Chuop[7], Phe Thong[8], Blandine Rammaert[9], Sopheak Hem[1], Johan van Griensven[2,8], Agus Rachmat[4], Thomas Fassier[10], Kruy Lim[8], Arnaud Tarantola[1]*

1 Epidemiology unit, Institut Pasteur du Cambodge, Phnom Penh, Cambodia, **2** Institute of Tropical Medicine, Antwerp, Belgium, **3** Angkor Hospital for Children, Siem Reap, Cambodia, **4** Naval Medical Research Unit2, Phnom Penh, Cambodia, **5** Wellcome Trust Major Overseas Programme, Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand, **6** Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Oxford University, Oxford, United Kingdom, **7** National Institute of Public Health, Phnom Penh, Cambodia, **8** Sihanouk Hospital Center of HOPE, Phnom Penh, Cambodia, **9** Hopital Necker-Enfants malades service des Maladies Infectieuses et Tropicales, APHP, Paris, France, **10** University of Health Sciences, Faculty of Medicine, Phnom Penh, Cambodia

PLoS One. 2014; 9(3): e89637

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PLoS One. 2014; 9(3): e89637

Further comment:

In two multinational antimicrobial susceptibility studies carried out between 2000 and 2004, **Vietnam's isolates had one of the highest resistance rates against cefuroxime, clindamycin, and erythromycin out of 11 Asian countries….**

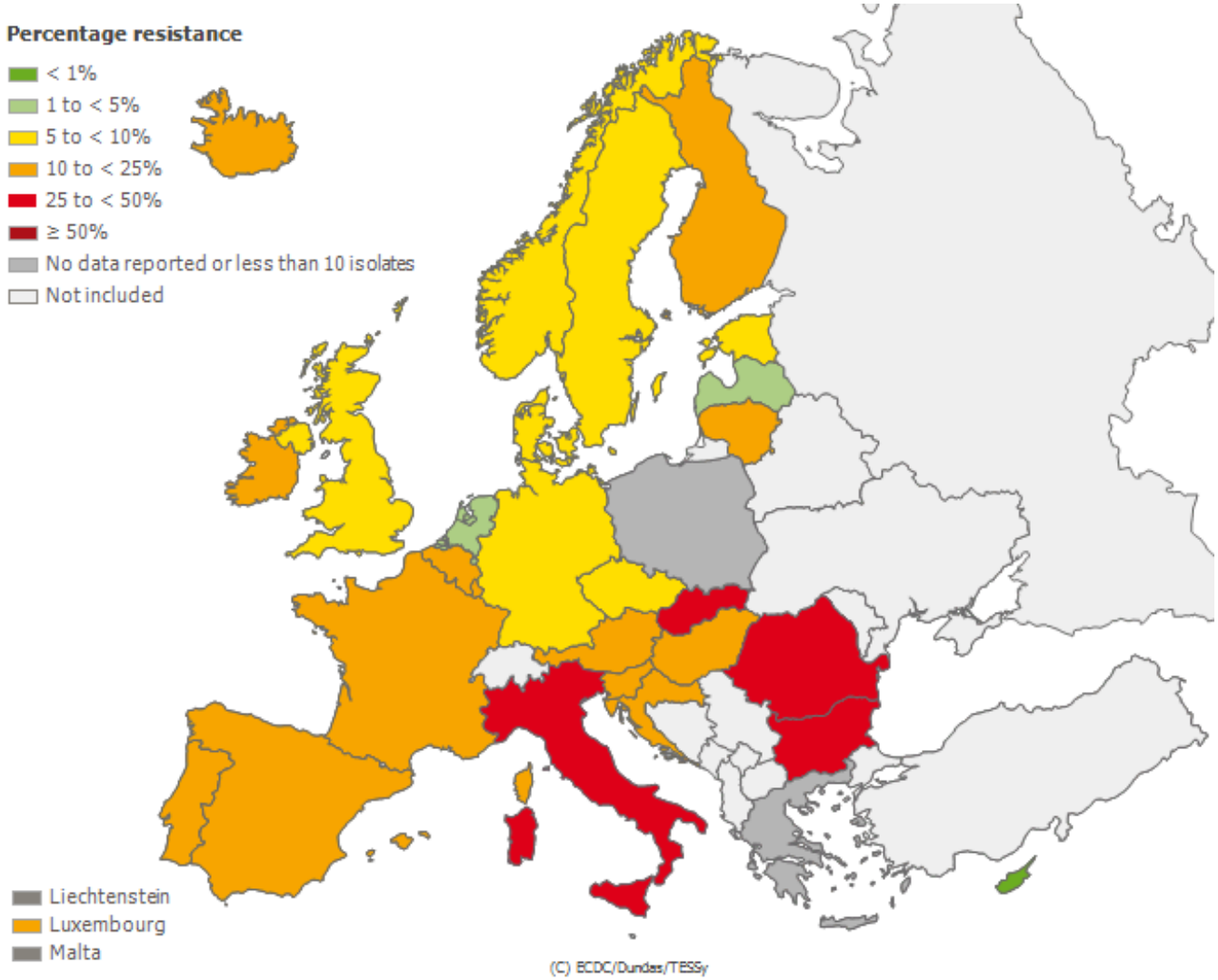
(cited from Hung et al. Int J Infect Dis. 2013; 17(6):e364-73.

Table 1. Antimicrobial resistance rates of *S. pneumonia.*

Antimicrobial agent	Mean resistance rate [b]			
study reference				
study period				
n. of isolates	n		N	%
penicillin G				
intermediate resistance	132	/	424	31.1
high level resistance	123	/	488	25.2
resistance (level not defined)	6	/	58	58.0
ampicillin	10	/	148	6.9
amoxicillin	5	/	84	6.0
amoxicillin-clavulanic acid	8	/	257	3.1
cefuroxime	122	/	257	47.5
ceftriaxone	22	/	224	9.8
cephalothin	0	/	64	0.0
cefotaxime	57	/	284	20.2
chloramphenicol	188	/	390	48.3
tetracycline	58	/	164	35.2
erythromycine	233	/	447	52.1
azithromycin	99	/	200	49.5
vancomycin	2	/	84	2.0
thrimetoprim/sulfamethoxazole	329	/	421	78.2
ofloxacin	75	/	200	37.5
levofloxacine	2	/	216	0.9

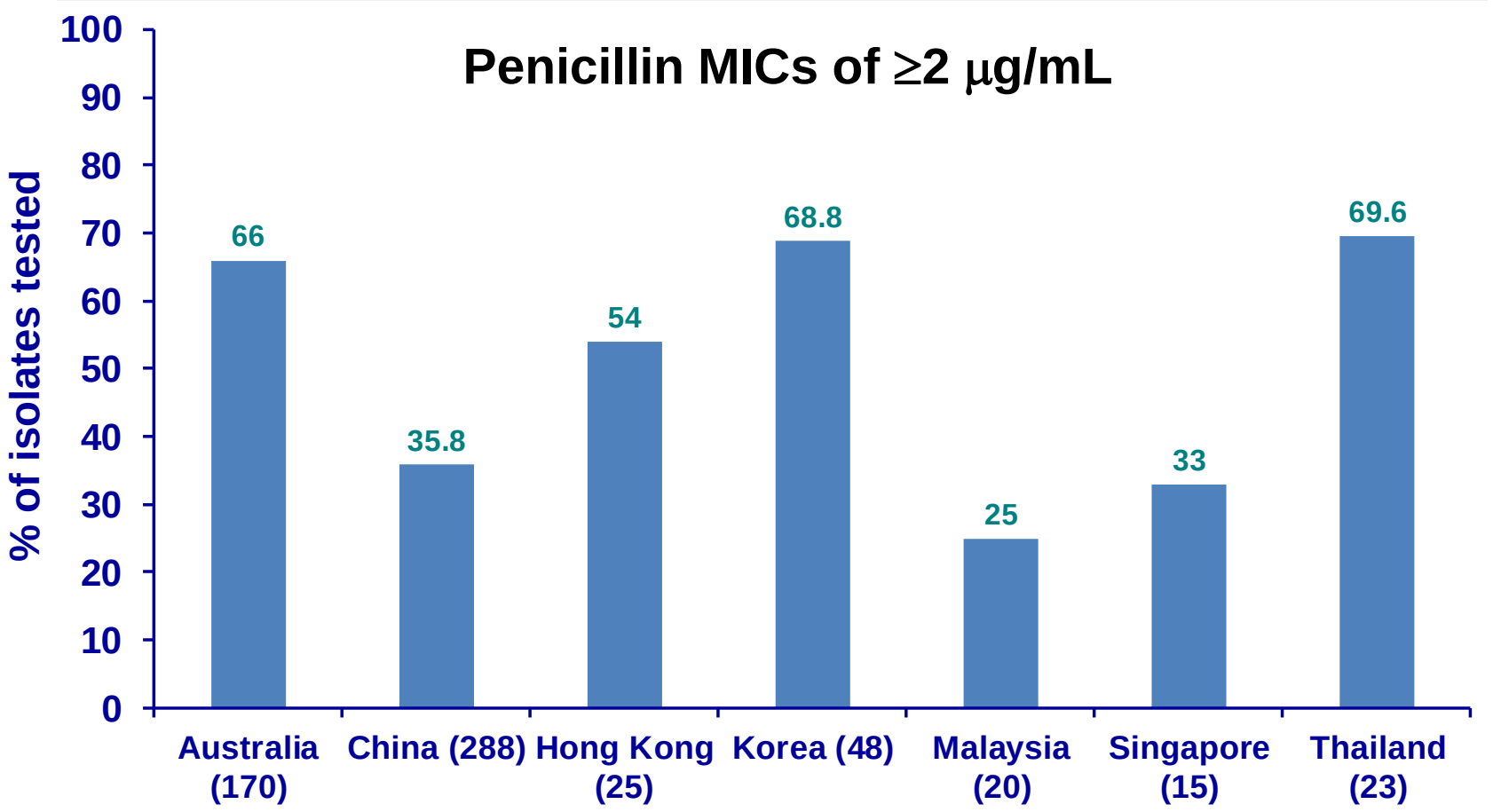
You are not alone … for macrolide resistance

Resistance to macrolides in Europe in 2014



http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx
Last visited: 14 March 2016

Resistance Rates of *S. pneumoniae*
Asia-Pacific Region



Sader et al. Diagn Microbiol Infect Dis 2013; 76:61-8.

Resistance to penicillin in Vietnam: 1. Hospital

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

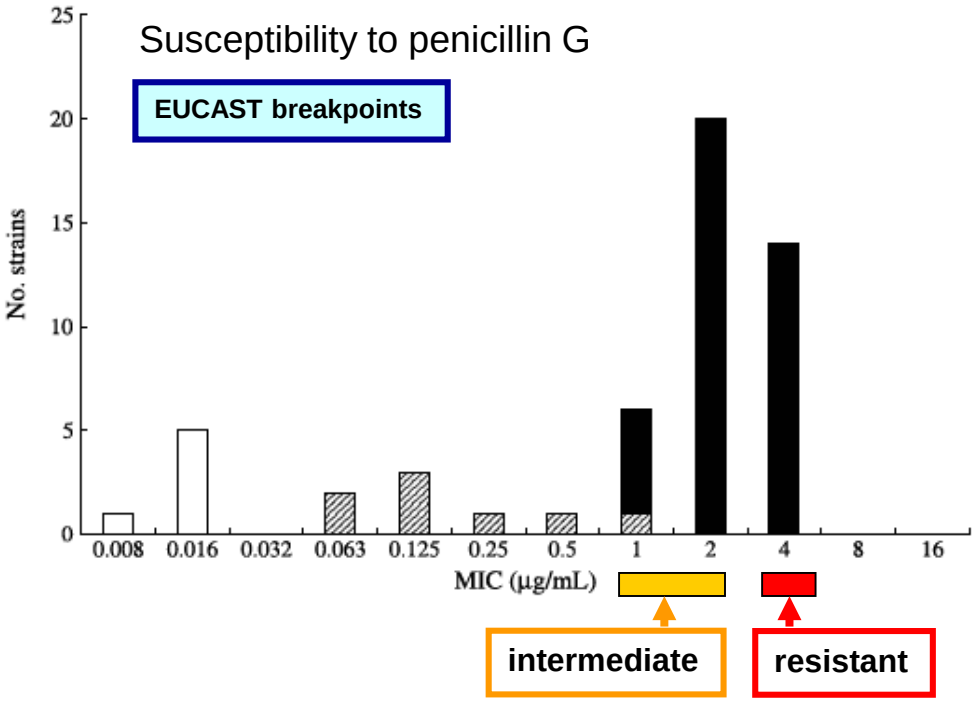
Original Article

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 to pencillin for *S. pneumoniae* at Bach Mai, Hanoi, Vietnam



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

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

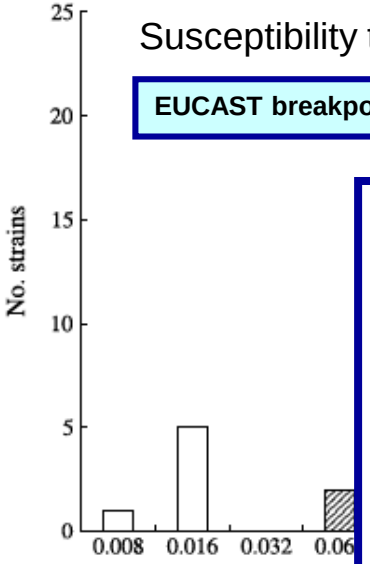


Table 2 Genotype of drug-resistant genes and MIC in 53 strains of *Streptococcus pneumoniae*

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

Recent Vietnamese data for respiratory tract infections in a major 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) *Unpublished data*

Resistance to penicillin in Vietnam: 2. 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

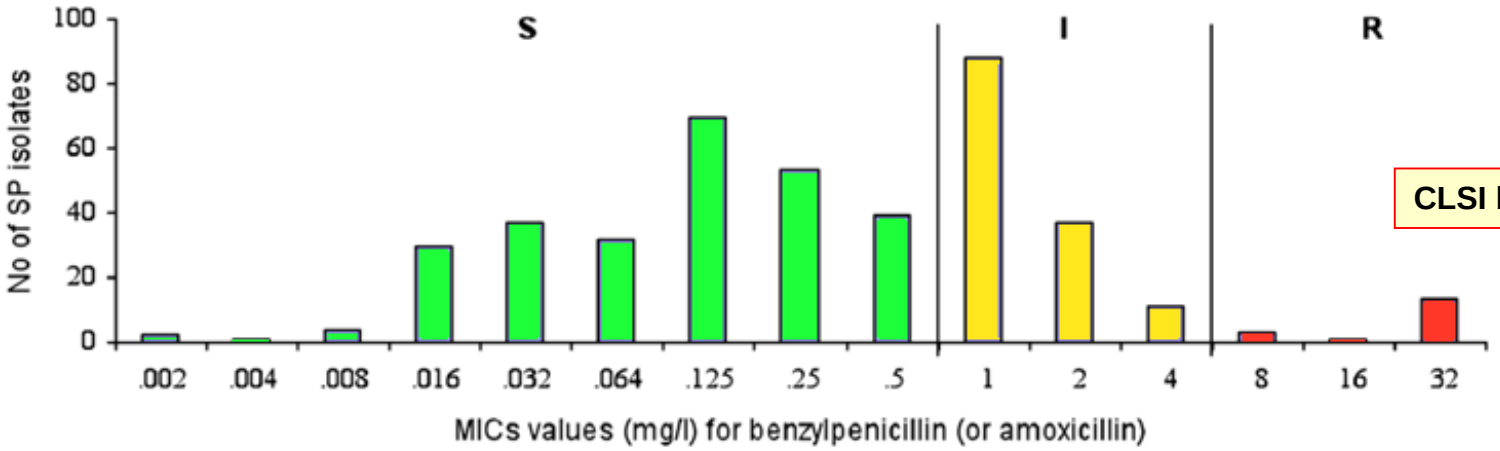
Decreased *Streptococcus pneumoniae* susceptibility to oral antibiotics among children in rural Vietnam: a community study

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



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 …

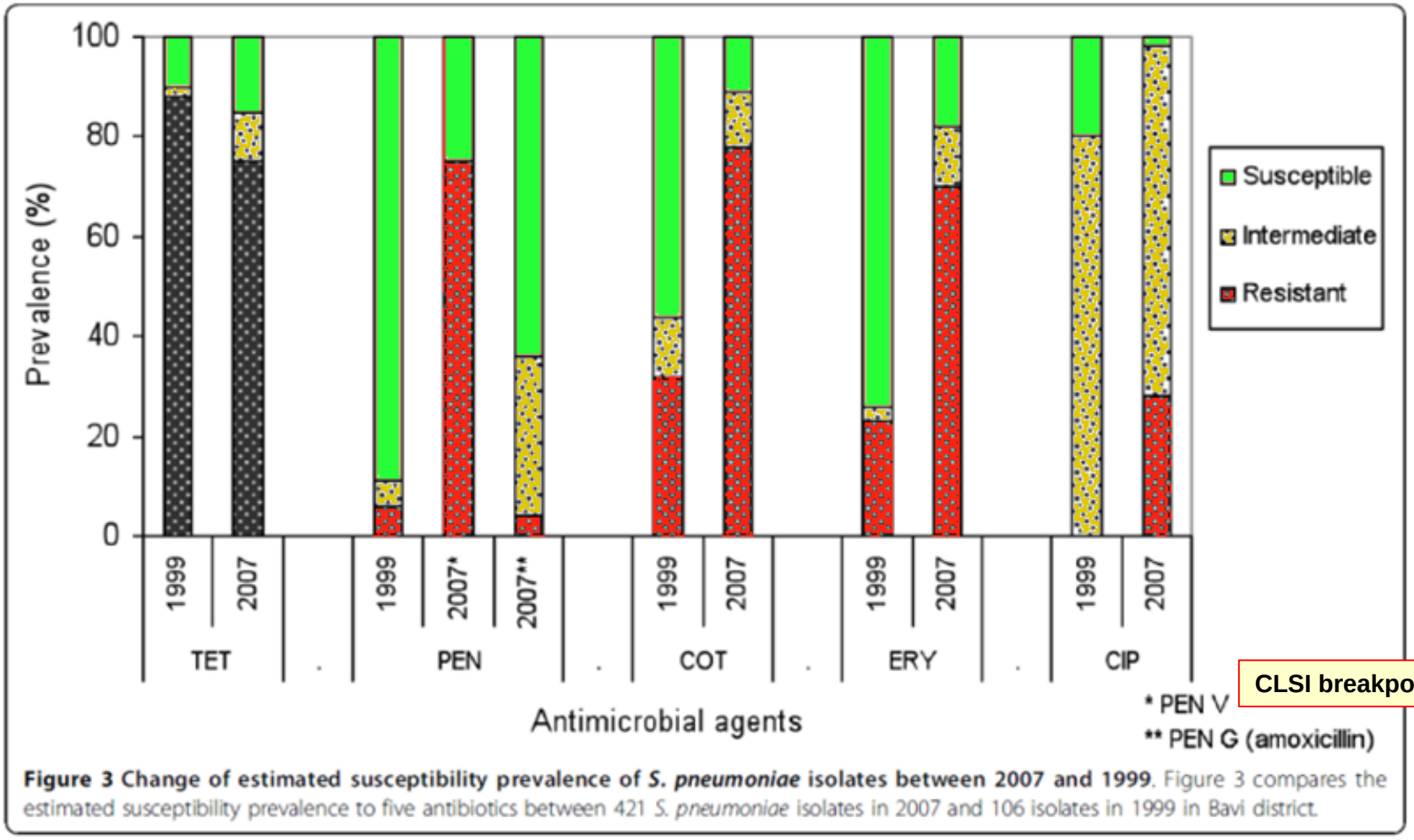


Figure 3 Change of estimated susceptibility prevalence of *S. pneumoniae* isolates between 2007 and 1999. Figure 3 compares the estimated susceptibility prevalence to five antibiotics between 421 *S. pneumoniae* isolates in 2007 and 106 isolates in 1999 in Bavi district.

CLSI breakpoints

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.

The message: make and use surveys

- Viet Nam should know ITS resistance patterns (by regions) !

Contents of the presentation

- The diseases and the enemies
- From enemies to antibiotics: which ones to use ?
- The fear for resistance…
- Epidemiology
- **Conclusions and Recommendations**

Conclusions and Recommendations

Any prescription should assess…

- the **risk/benefit balance** for **individual patients**
- the **adequacy to the most likely pathogen** (with possibility for surprises !)
- the current and foreseeable **resistance to antibiotics** that will **affect all present and future patients**

https://www.whitehalltraining.com/blog/risk-benefit-doesnt-balance

Please, ask questions… and start the discussion…

I'll do my best

Back-up

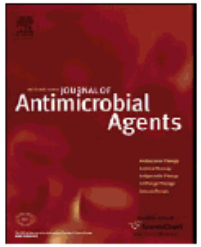
The hidden risk of therapy (in our hospitals …)

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

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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]

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[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*
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[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*

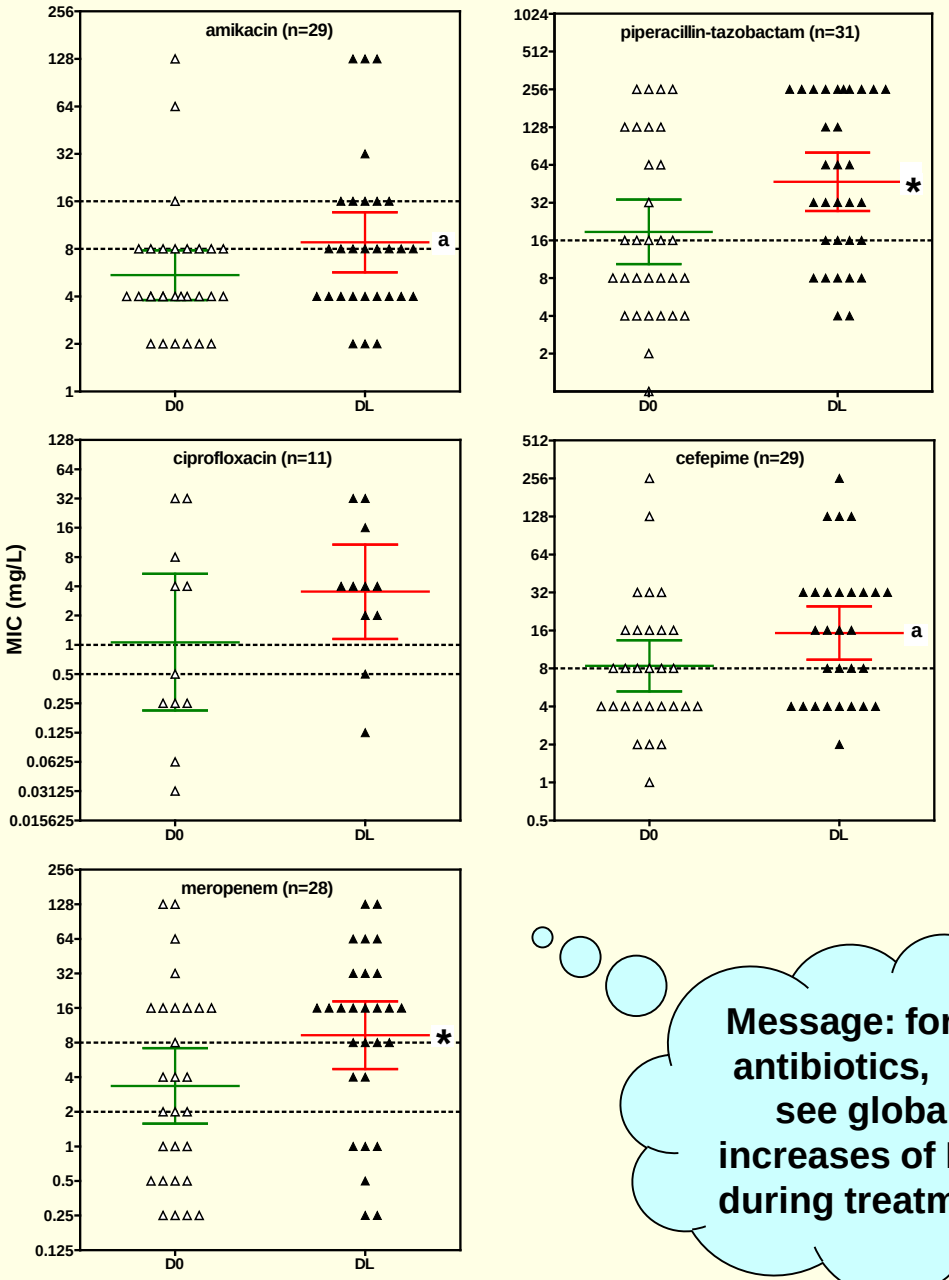
Do you remain effective while treating ?

- 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

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 ≤ 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

S. pneumoniae: example in Belgium for CAP

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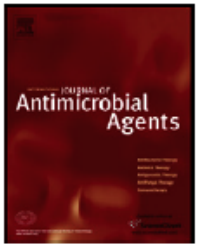

Antimicrobial susceptibility of *Streptococcus pneumoniae* isolates from vaccinated and non-vaccinated patients with a clinically confirmed diagnosis of community-acquired pneumonia in Belgium

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]

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[d] *Microbiologie en ziekenhuishygiëne, Universitair Ziekenhuis Brussel, Brussels, Belgium*
[e] *Afdeling pneumologie, O.L.V. Ziekenhuis, Aalst, Belgium*
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[h] *Service des urgences, Cliniques universitaires Saint-Luc, Brussels, Belgium*
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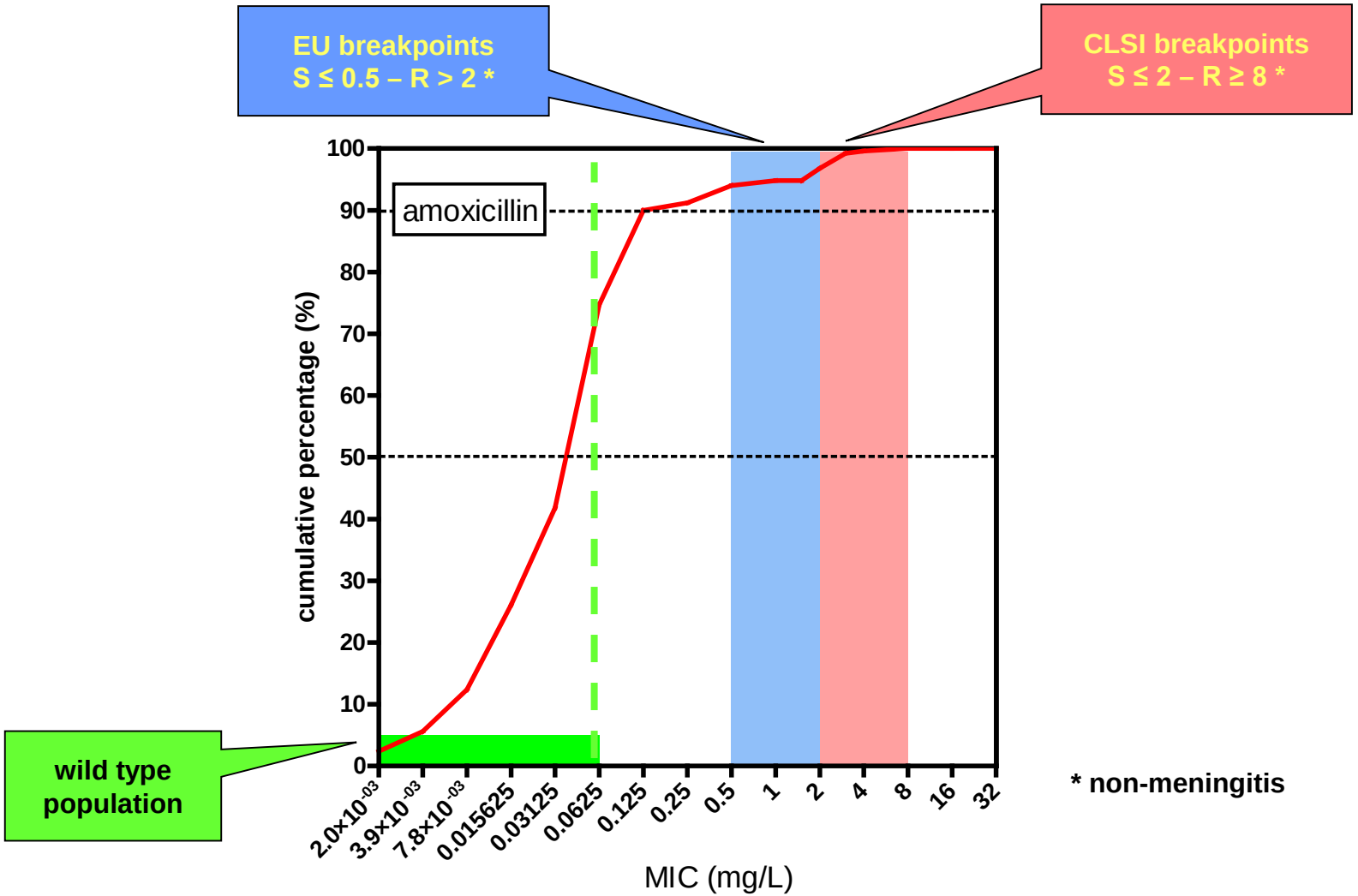
[j] *Laboratoire de microbiologie, CHU Mont-Godinne, Yvoir, Belgium*

S. pneumoniae: an example in Belgium for CAP



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

S. pneumoniae: how to make antibiotic policy