The misuse of antibiotics in the management of respiratory infections and its consequences

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Indonesia and Vietnam Masterclass
Geneva, Switzerland - 1st October 2015

With authorization of the Common Belgian Ethical platform (visa no. 15/V1/7937/071695)

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

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

Which burden ?

- COPD
  - defined as a disease characterized and diagnosed by spirometric measurement of airflow limitation that is not fully reversible [1]
  - also a major cause of death (4th in 2006 and projected 3rd in 2020) [2]
  - runs as often undiagnosed at early stages [2]
  - "progresses" to decrease of respiratory function (worsens) triggered by successive/frequent infectious exacerbations [3]

[1] Celli BR, MacNee W: Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J. 23:932-946 2004 // See also "Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2015) from GOLD (http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf)

[2] Mannino DM, Braman S: The epidemiology and economics of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 4:502-506 2007 Fry *et al.* JAMA. 294:2712-2719 2005 // Kung HC, Hoyert DL, Xu J, et al.: Deaths: Final data for 2005. Natl Vital Stat Rep. 56:1-120 2008

[3] Anzueto A, Sethi S, Martinez FJ: Exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 4:554-564 2007

Which burden ?

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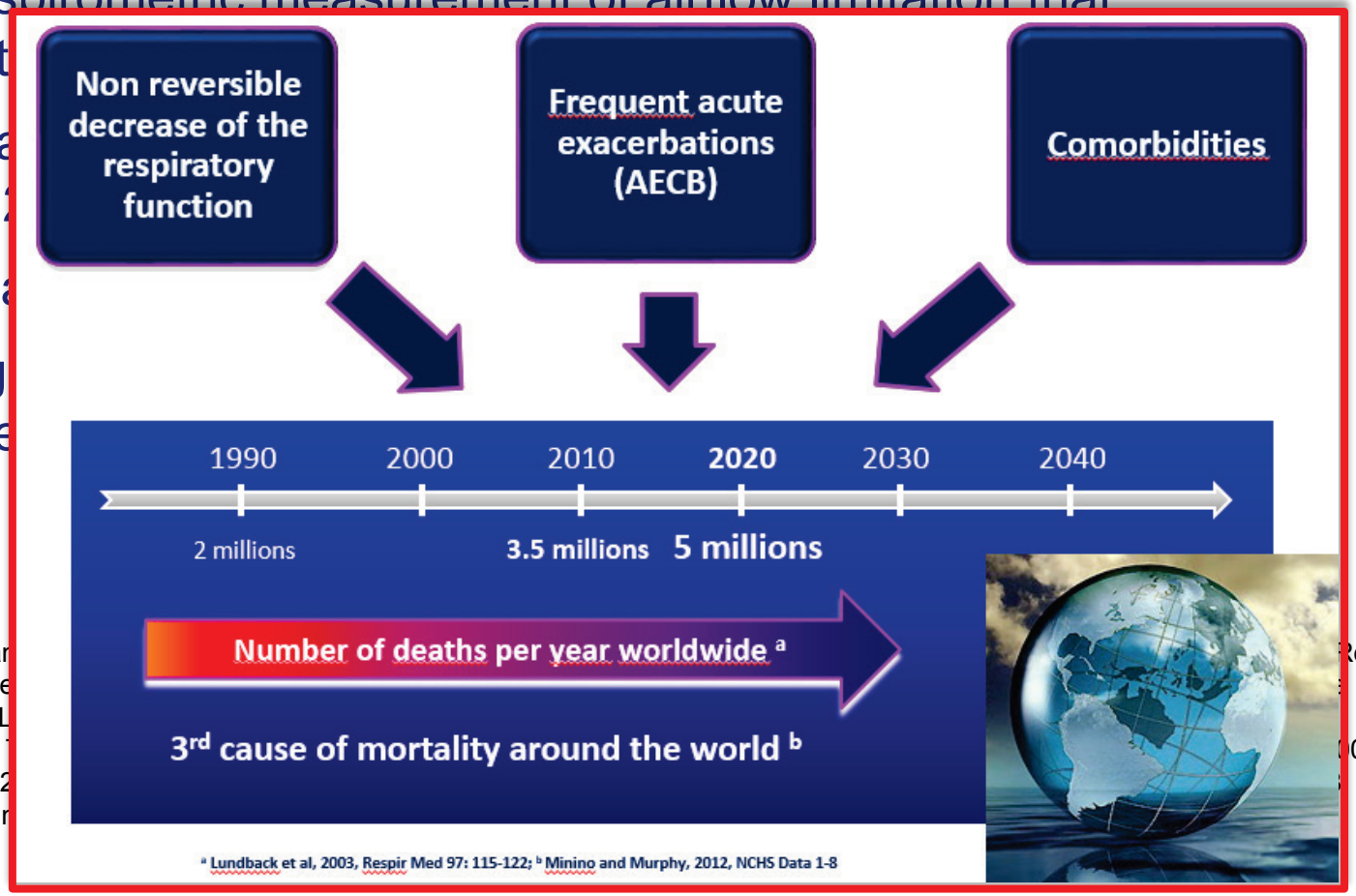
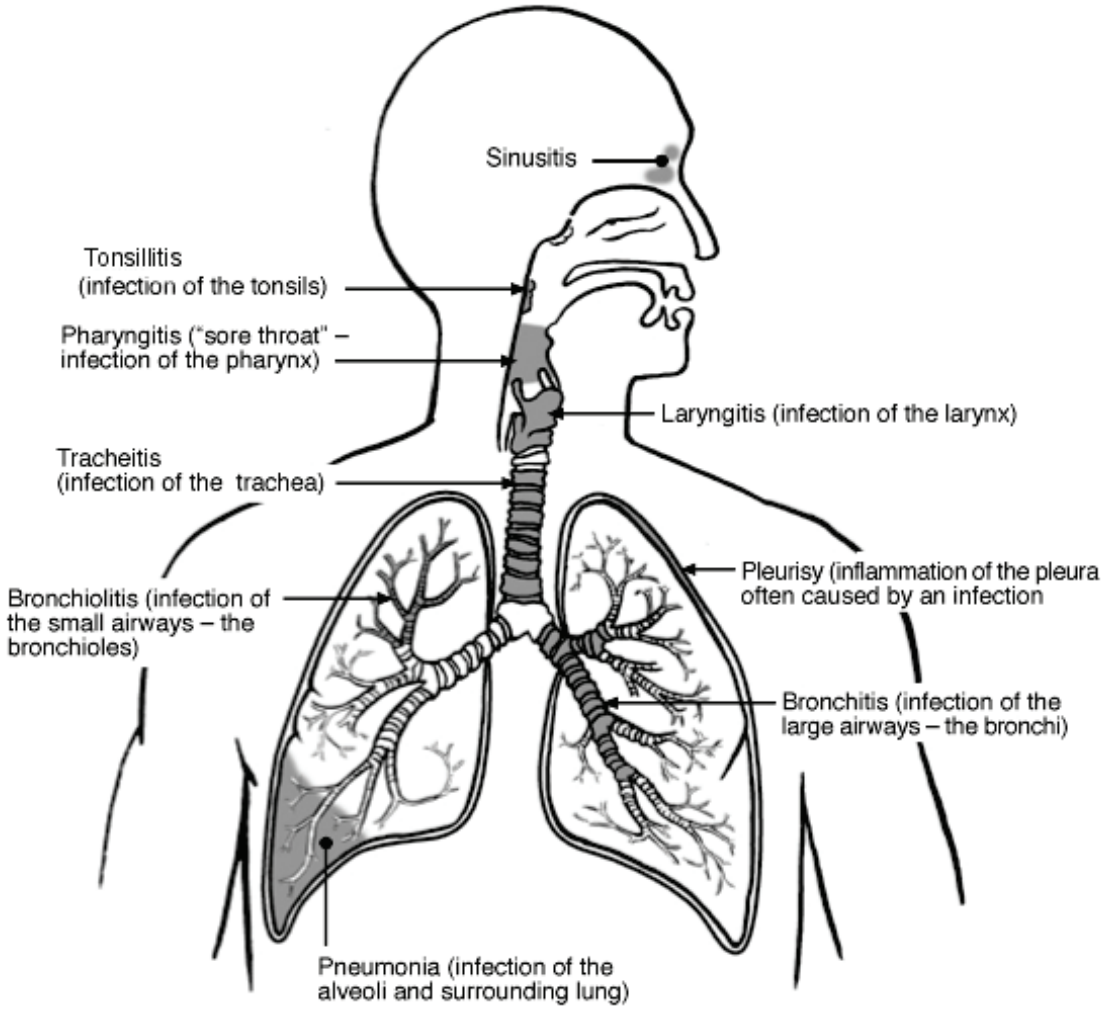


[1] Celli BR, MacNee W: Star Respir J. 23:932-946 2004 // See (updated 2015) from GOL
[2] Mannino DM, Braman S: 07 Fry *et al.* JAMA. 294:2712
[3] Anzueto A, Sethi S, Martin

Contents of the presentation

- **The diseases and the enemies**
- **From enemies to antibiotics: which ones to use ?**
- **Collateral effects**
  - Patient: toxic effects of antibiotics
  - Patient and population: alteration of the flora
  - Population: emergence of resistance
    - General concepts (resistome, selectome, inappropriate usage)
    - Situation in Asia (epidemiology)
- **Conclusions and Recommendation**

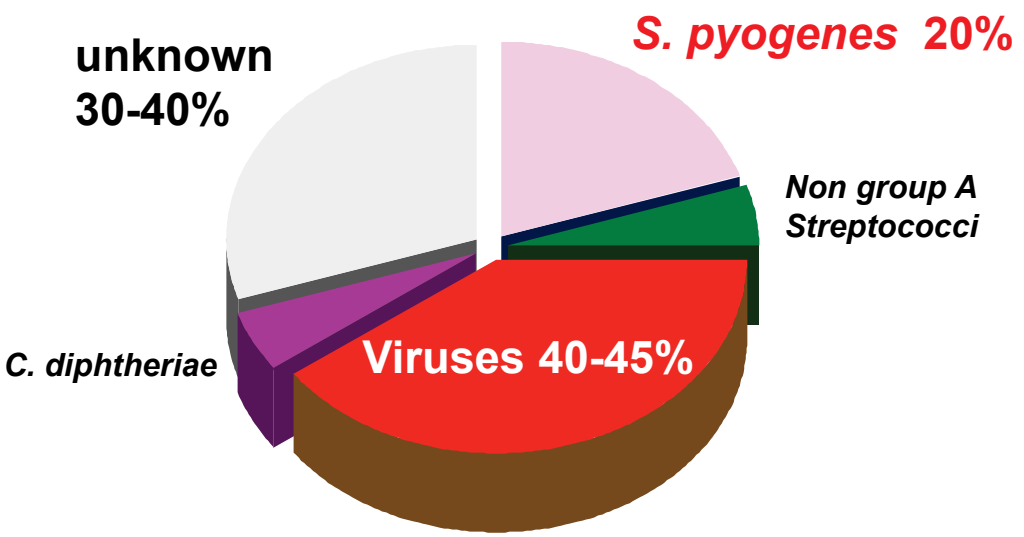
Respiratory tract infections: 1. the diseases



Infections of the respiratory tract

Respiratory tract infections: 2. the enemies

1. pharyngitis



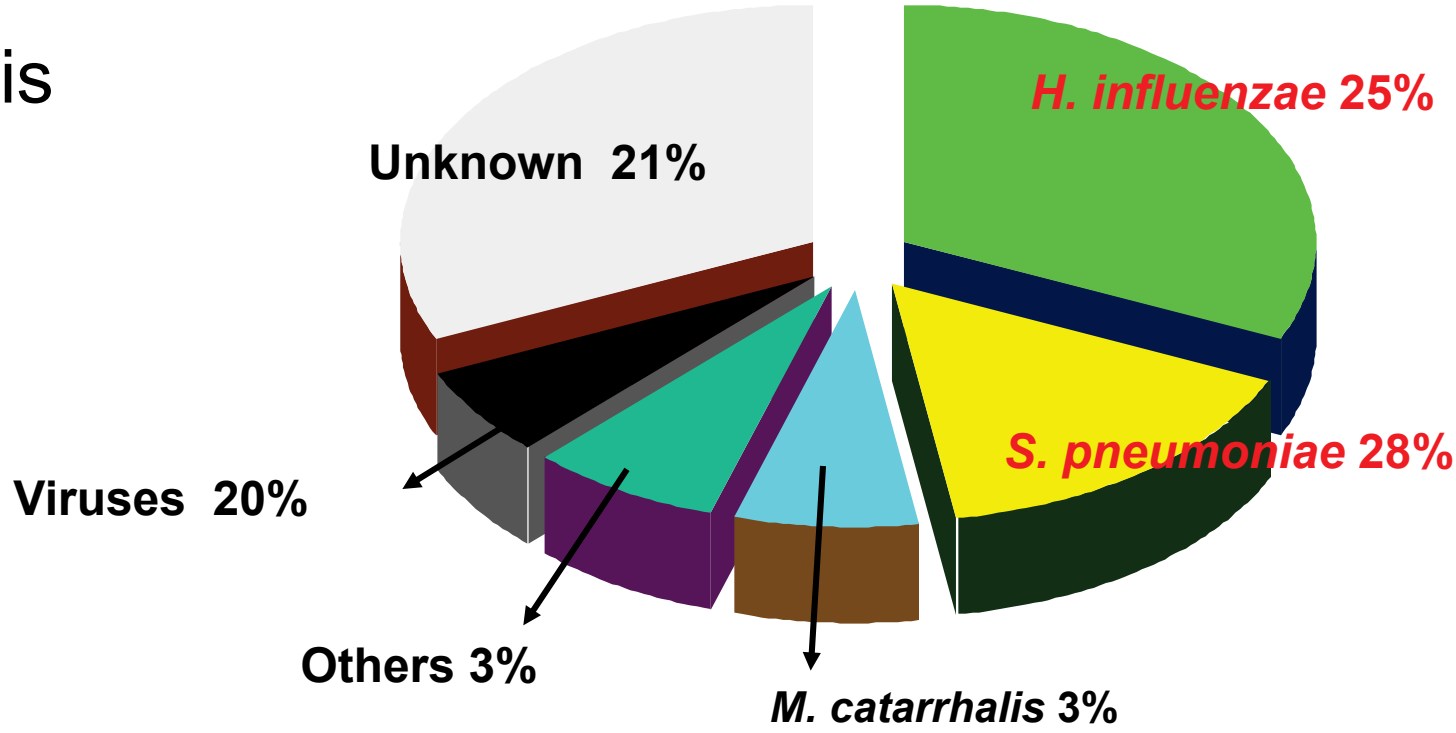
- Between **49% and 57% of children and 64% of adults evaluated for pharyngitis receive an antibiotic prescription**, which is a rate much higher than the prevalence of *S. pyogenes* infection for which treatment is indicated
- In addition, recent surveys demonstrated a significant **increase in the use of broad-spectrum antibiotics** for the treatment of pharyngitis, a practice that is thought to contribute to the growing problem of antibiotic resistance and the "medicalization" of a generally benign illness

References
- Linder *et al.*: Antibiotic treatment of children with sore throat. JAMA. 294:2315-2322 2005 PMID: 16278359
- Nash *et al.*: Antibiotic prescribing by primary care physicians for children with upper respiratory tract infections. Arch Pediatr Adolesc Med. 156:1114-1119 2002 PMID: 12413339
- Steinman *et al.*: Changing use of antibiotics in community-based outpatient practice, 1991-1999. Ann Intern Med. 138:525-533 2003 PMID: 12667022

Modified from Flores & Caserta. Pharyngitis *In* Principles and Practice of Infectious Diseases, Mandell *et al.* eds, 8th Edition on line - chapter 59 (available on line at https://expertconsult.inkling.com/read/mandell-douglas-bennetts-infectious-diseases-8/chapter-59/pharyngitis)

Respiratory tract infections: 2. the enemies

2. otitis



Many children have AOM caused by a viral pathogen and may resolve **without antibacterial drugs**.

References

- Van Buchem et al. Therapy of acute otitis media: myringotomy, antibiotics or neither? A double-blind study in children. Lancet. 2:883-887,1981 PMID:6117681
- Browning GG: Childhood otalgia: acute otitis media. Br Med J. 300:1005-1007, 1990

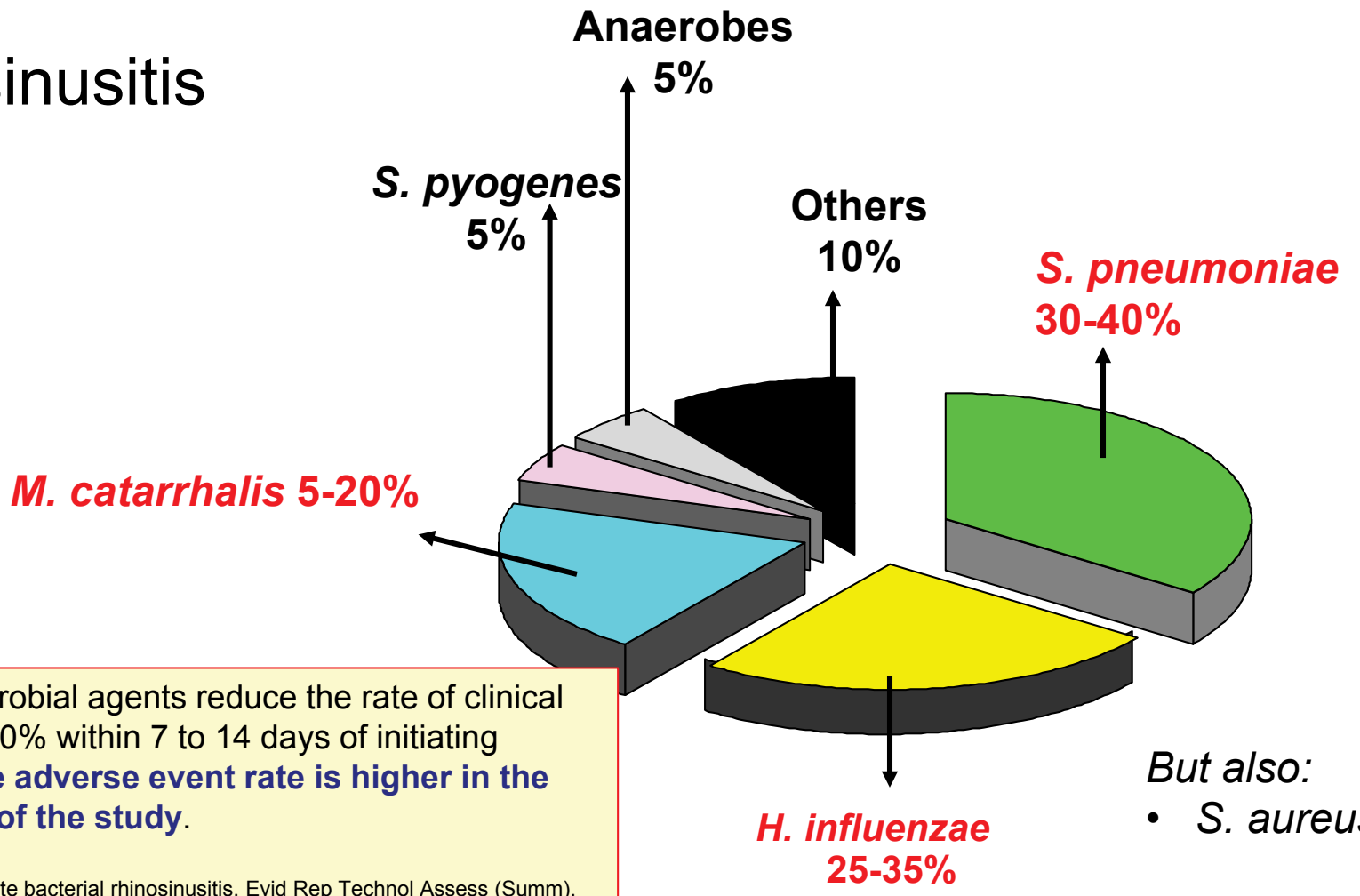
But also:

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

Data modified from Casey & Pichichero M. Changes in frequency and pathogens causing acute otitis media in 1995-2003. *Pediatr Infect Dis J.* 2004; 23:824-828.

Respiratory tract infections: 2. the enemies

3. sinusitis



Overall, antimicrobial agents reduce the rate of clinical failure 25% to 30% within 7 to 14 days of initiating therapy, **but the adverse event rate is higher in the antibiotic arm of the study**.

References

- Ip et al. Update on acute bacterial rhinosinusitis. Evid Rep Technol Assess (Summ). 2005 1-3
- Anon et al.: Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg. 130:1-45, 2004 PMID:14726904

From DeMuri & Wald, Sinusitis *In* Principles and Practice of Infectious Diseases, Mandell *et al.* eds, 7th Edition on line - chapter 58 (https://expertconsult.inkling.com/read/principles-practice-infectious-diseases-mandell-7th/chapter-58/sinusitis)

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

Respiratory tract infections: 2. the enemies

4. Pneumonia: which type ?

- **community acquired (CAP)**
  - Children
  - Young adult patients with no risk factor
  - 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**
Streptococcus pneumoniae	**19.3**
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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

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)

Respiratory tract infections: 2. the enemies

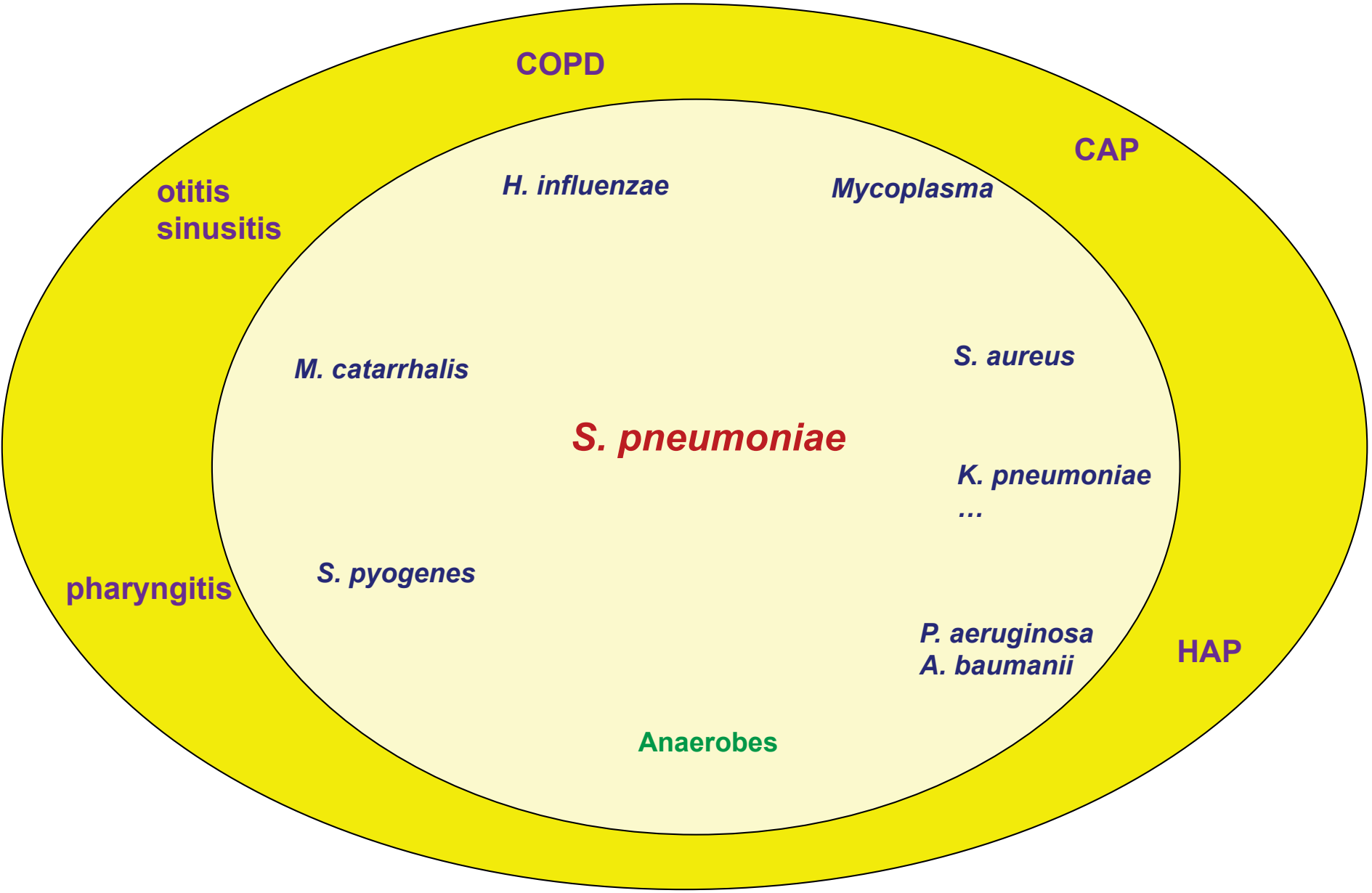
5. Chronic obstructive lung disease (COPD)

- **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

- Celli BR, MacNee W: Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J. 23:932-946 2004
- "Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease" (updated 2015) from GOLD (http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf)
- Punturieri *et al.* Chronic obstructive pulmonary disease and acute excerbations *In* Priciples and Practie of Infectious Diseases, Mandell et al. eds, 7th Edition on line - chapter 62 (https://expertconsult.inkling.com/read/principles-practice-infectious-diseases-mandell-7th/chapter-62/exacerbations-of-chronic#3b35b297312346c69aede023c9145ce4)

In a nutshell (for bacteria) …

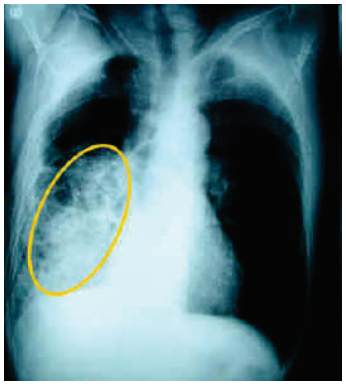


From enemies to antibiotics…

Classical antibiotic therapies

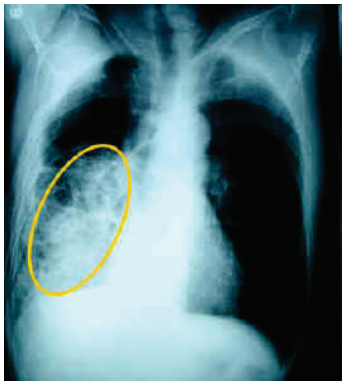
- β-lactam antibiotics
  - Penicillin, amoxicillin (+/- clavulanic acid), piperacillin …
  - Cephalosporins (2d, 3d generation….)
  - Carbapenems
- Macrolides (clarithromycin, azithromycin, …)
- Tetracyclines
- Fluoroquinolones
  - Respiratory fluoroquinolones: levofloxacin, moxifloxacin, gemifloxacin…
  - Anti Gram-negative: ciprofloxacin, levofloxacin
- Vancomycin

We all agree about efficacy towards susceptible bacteria…



→ **Antibiotic therapy !**

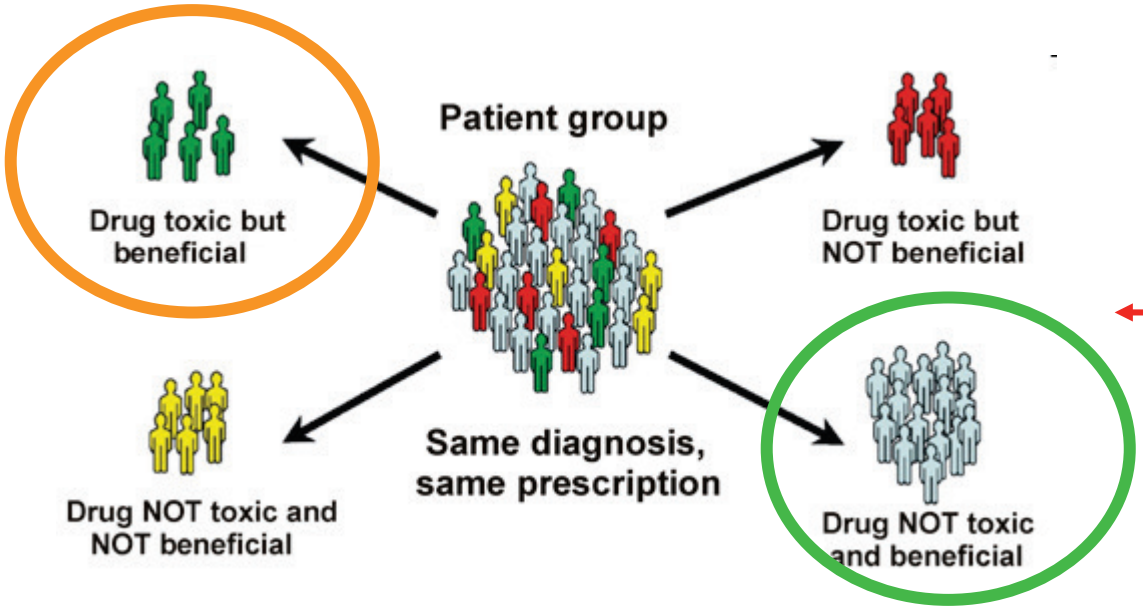
We all agree about efficacy towards susceptible bacteria…



→ **Antibiotic therapy !**

↓

side effects ?



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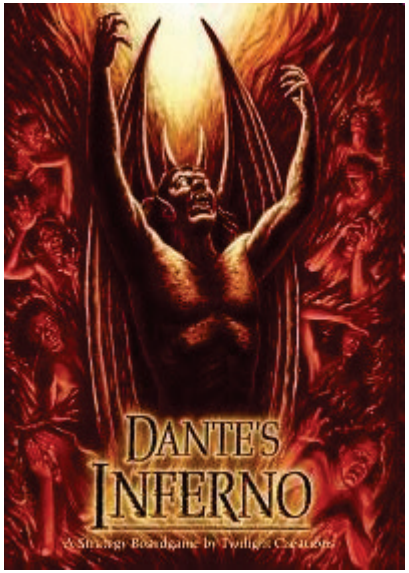

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
β-lactams	**amoxicillin**	• **Anaphylactic reactions** ← • *Clostridium difficile*-associated colitis • Digestive tract: diarrhoea, nausea • CNS: agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness.
	amoxicillin – clavulanic acid	• **Anaphylactic reactions** ← • *Clostridium difficile*-associated colitis • **Hepatic toxicity, including hepatitis and cholestatic jaundice** ← • Digestive tract: diarrhoea, nausea • CNS : agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness
	cefuroxime	• **Anaphylactic reactions and cutaneous eruptions** ← • Nephrotoxicity (aggrav. with loop diuretics) • Hepatic toxicity • *Clostridium difficile*-associated colitis
	ceftriaxone	• **Anaphylactic reactions and cutaneous eruptions** ← • Digestive tract:diarrhoea, nausea • *Clostridium difficile*-associated colitis • Hematologic disturbances (éosinophilia, leucopenia, granulopenia, thrombopenia) • Hepatic and biliary toxicities (precipitation of Ca^{++} salt) • CNS: cephalalgia, vertigo

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

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
Macrolides	**clarithromycin**	• Anaphylactic reactions • *Clostridium difficile*-associated colitis • **Drug interactions (CYP450)** • **Hepatic toxicity, including hepatitis and cholestatic jaundice** • **Palpitations, arrhythmias including prolonged QTc** • Digestive tract: diarrhoea, nausea, vomiting, abnormal taste • CNS: headache, confusion, …
	azithromycin	• Anaphylactic reactions • *Clostridium difficile*-associated colitis • Drug interactions (CYP450), less frequent than with other macrolides • **Hepatic toxicity, including hepatitis and cholestatic jaundice** • Digestive tract: diarrhoea, nausea, abdominal pain • CNS: dizziness, fatigue, vertigo, … • Genitourinary: nephritis, vaginitis
	telithromycin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • **Hepatotoxicity** • Visual disturbance • Loss of consciousness • Respiratory failure in patients with myastenia gravis • **QTc prolongation** • **Drug interactions (CYP450)** • Digestive tract: diarrhoea, nausea, vomiting, dysgueusia • CNS: headache, dizziness

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

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
tetracyclines	doxycycline	• **Anaphylactic reactions and allergic skin reactions**  • *Clostridium difficile*-associated colitis • Digestive tract: anorexia, glossitis, dysphagia, nausea, vomiting, diarrhoea • **esophagitis and esophageal ulcerations**  • Blood cells: hemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia • Hepatotoxicity • **Photosensitivity** 

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

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
fluoroquinolones	levofloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • Hematologic toxicity • **Hepatotoxicity (ALT-AST elevation [common])** • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Musculoskeletal: tendinopathies** • Peripheral neuropathy • Prolongation of the QTc interval (cardiac disorders [rare]) • **Hypoglycaemia (rare)** • **Digestive tract: nausea, diarrhoea**
	moxifloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • **Hepatotoxicity (ALT-AST elevation [common])** • **Musculoskeletal: Tendinopathies** • Peripheral neuropathy • Prolongation of the QT interval (cardiac disorders [rare]) • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Digestive tract: nausea, diarrhoea**

* based on an analysis of the current respective labelling (European SmPC)
- common: 1/10 to 1/100
- rare: 1/1000-1/10000

Note: the current EU SmPCs of levofloxacin (TAVANIC®) and of moxifloxacin state:

- *For [community-acquired pneumonia],* TAVANIC® *should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.*
- *Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.*

Carbonelle *et al.*, in preparation

All antimicrobials have associated risks

Conclusions so far:

- All antimicrobials used in RTI are associated with known toxicities
- The main point will be the recognition of patients at risk (exclusions)
- The next point will be a correct evaluation of the benefit / risk ratio in the **specific environment** and for the **specific patient**

Never say that …

and check for specific risks

RTI: respiratory tract infection

Beyond toxic effects:

- Perturbation of the normal flora
  - Intestinal microbiome
  - Respiratory microbiome

https://www.pinterest.com/edtori/funny-gifts/

- Resistance

http://www.public.asu.edu/~shaydel/personnel.html

Perturbation of the normal flora: focus on respiratory microbiome

rstb.royalsocietypublishing.org

Review

Cite this article: de Steenhuijsen Piters WAA, Sanders EAM, Bogaert D. 2015 The role of the local microbial ecosystem in respiratory health and disease. *Phil. Trans. R. Soc. B* **370**: 20140294.
http://dx.doi.org/10.1098/rstb.2014.0294

PHILOSOPHICAL TRANSACTIONS B

The role of the local microbial ecosystem in respiratory health and disease

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[1]Department of Paediatric Immunology and Infectious Diseases, The Wilhelmina Children's Hospital/University Medical Centre Utrecht, Utrecht, The Netherlands
[2]Centre for Infectious Disease Control, National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Perturbation of the normal flora: focus on respiratory microbiome

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Review

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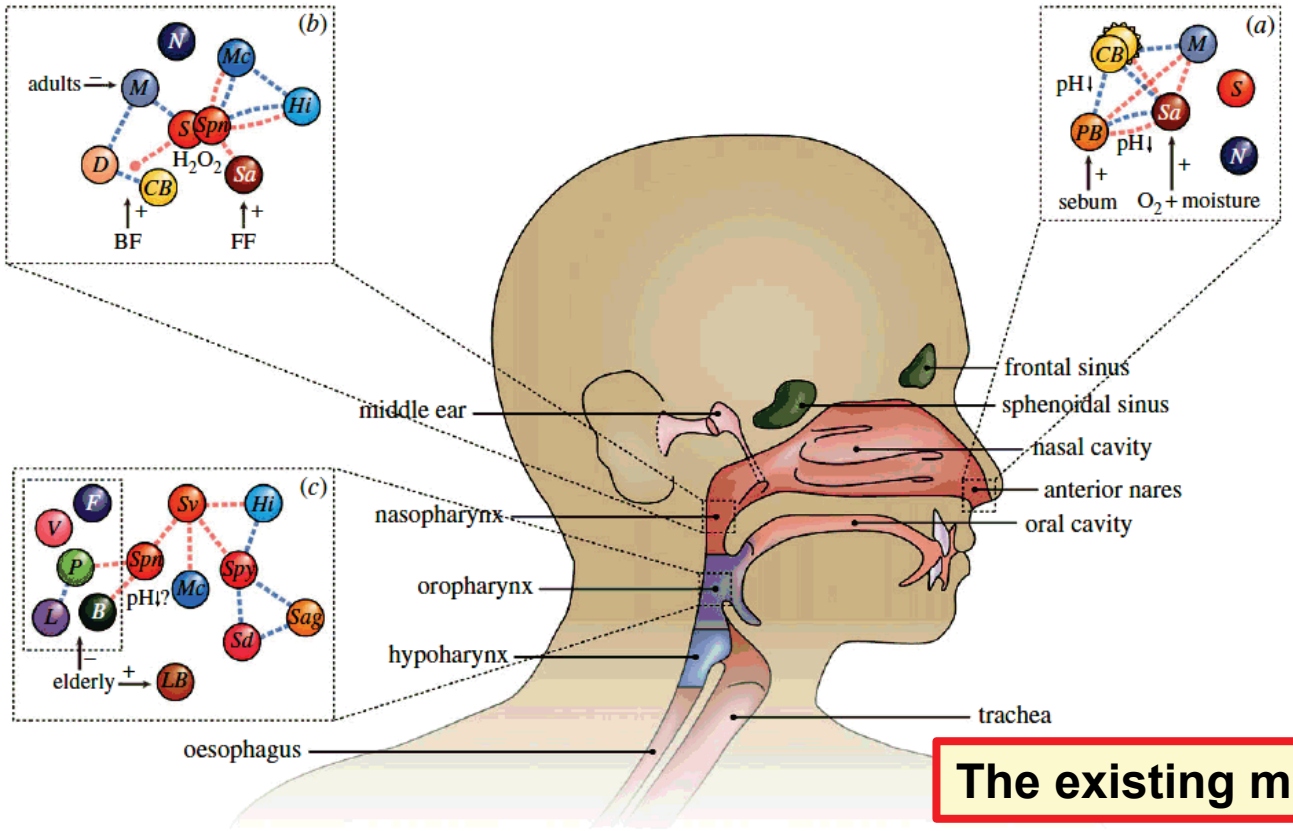


The existing microbiome

Figure 1. Niche-specific bacterial community structure of the anterior nares, the nasopharynx and the oropharynx (which resembles the oral cavity). Microbial interaction networks associated with these anatomical locations are depicted, with potential driving environmental forces (acidity, oxygen availability and presence of antimicrobial compounds). Coloured circles represent individual bacterial community members, which are interconnected by dotted blue and red lines, respectively, representing positive and negative associations. Microbial community members are colour-coded based on phylum level; Firmicutes: red/brown, Actinobacteria: yellow, Bacteroidetes: green, Proteobacteria: blue and Fusobacteria: purple. S: *Streptococcus* spp.; Spn: *S. pneumoniae*; Sv: *S. salivarius*; Spy: *S. pyogenes*; Sd: *S. dysgalactiae*; Sag: *S. agalactiae*; Sa: *S. aureus*; V: *Veillonella* spp.; D: *Dolosigranulum* spp.; LB: *Lactobacillus* spp.; CB: *Corynebacterium* spp.; PB: *Propionibacterium* spp.; B: Bacteroidetes; P: *Prevotella* spp.; *M*: *Moraxella* spp.; Mc: *M. catarrhalis*; Hi: *H. influenzae*; N: *Neisseria* spp.; L: *Leptotrichia* spp. and F: *Fusobacterium* spp.

Perturbation of the normal flora: focus on respiratory microbiome

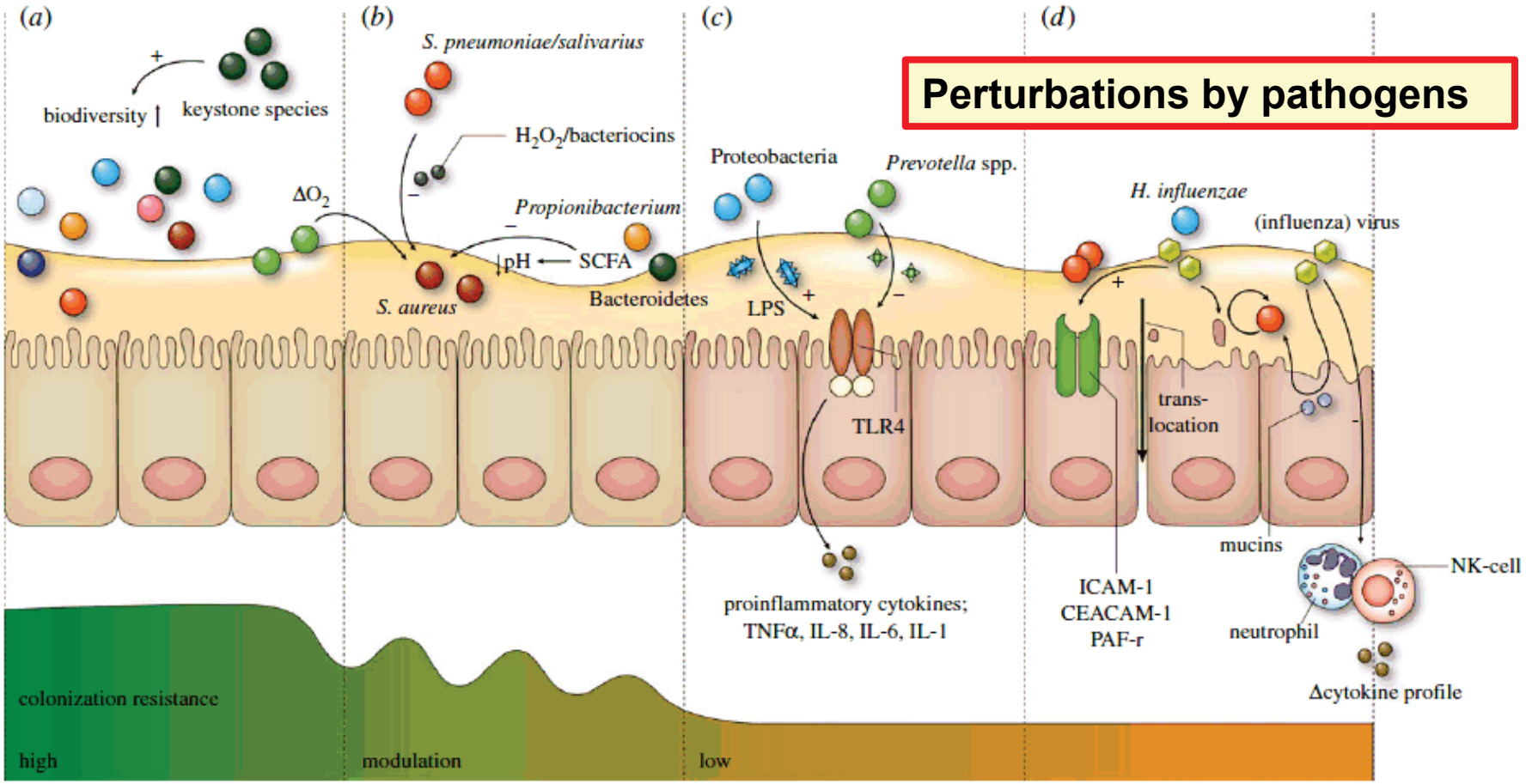
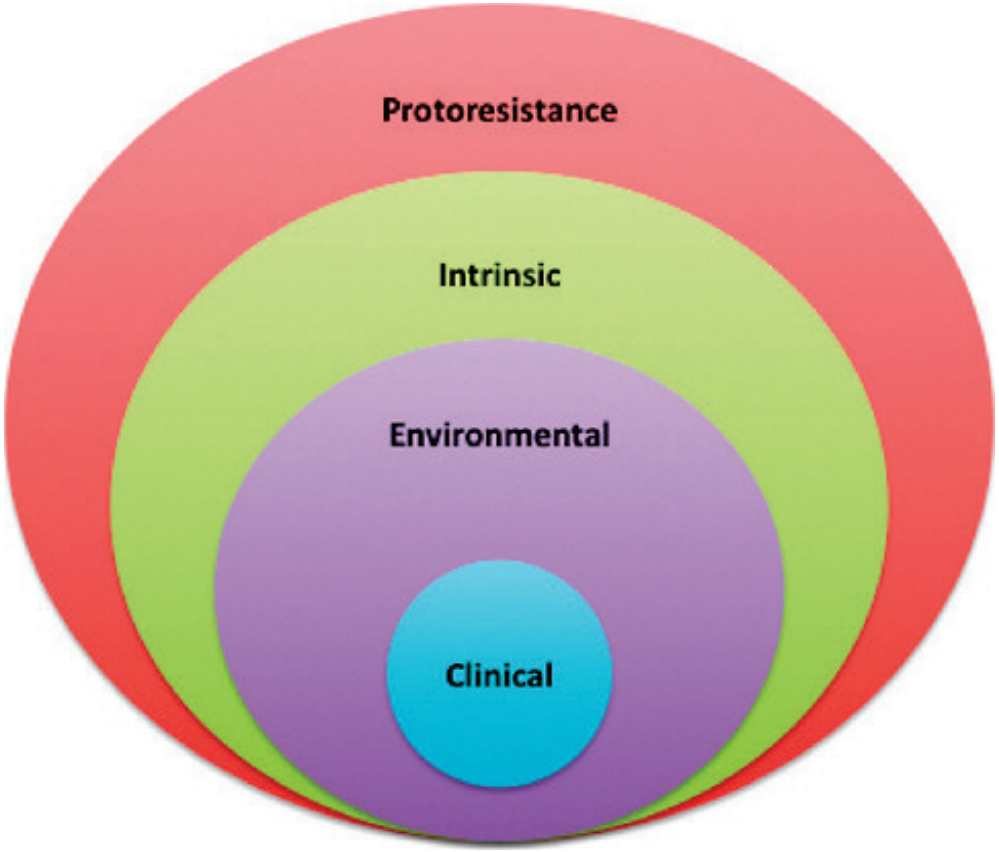


Figure 2. Hypothetical model on the relationship between the URT microbiome and pathogenesis of infectious respiratory diseases.

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 linked to antibiotic use
  - **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 …

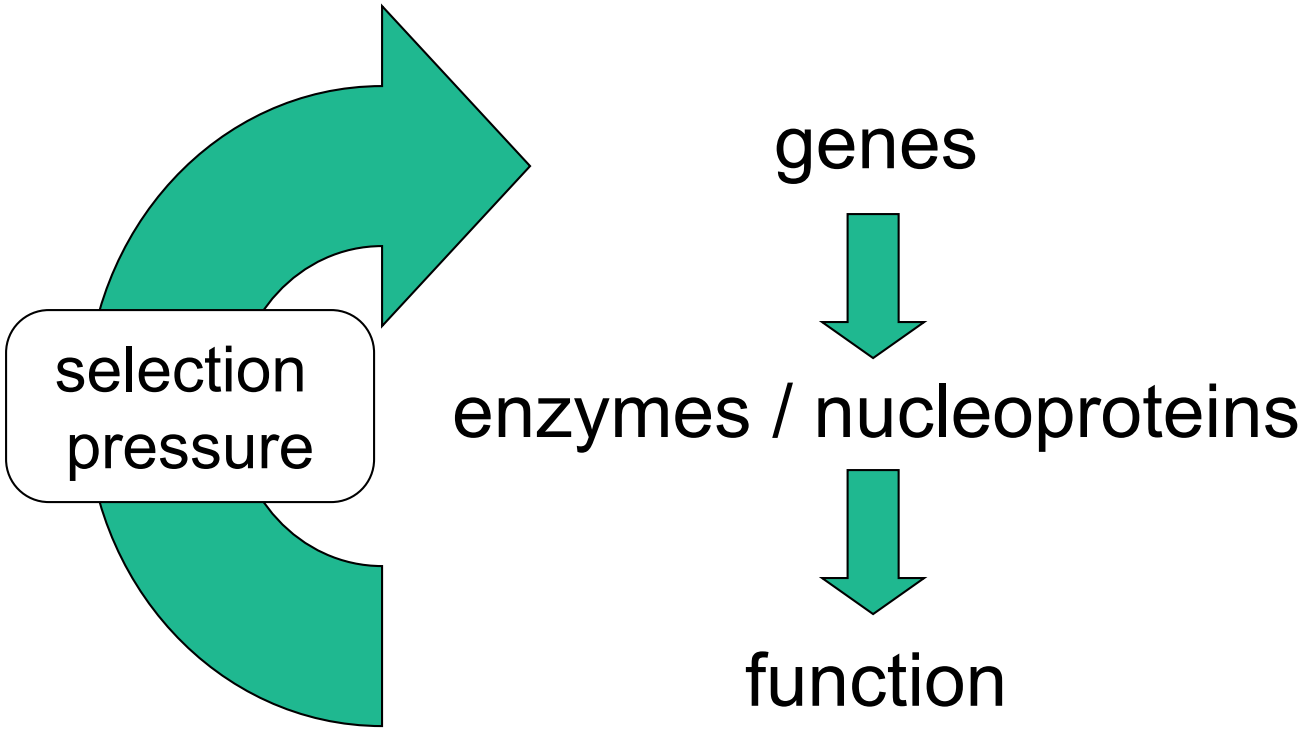


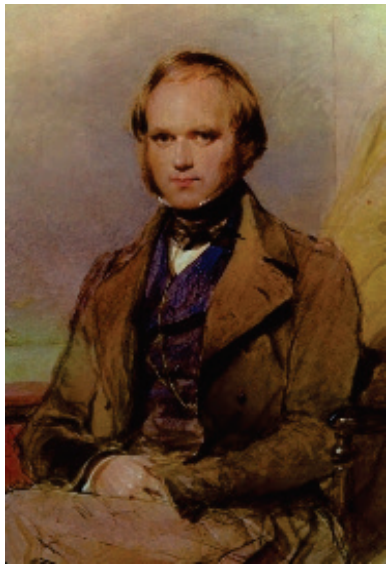
- all the genes and their products that contribute to antibiotic resistance
- highly redundant and interlocked system
- clinical resistance under represents the resistance capacity of bacteria
- existing biochemical mechanisms (protoresistome) serve as a deep reservoir of precursors that can be co-opted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

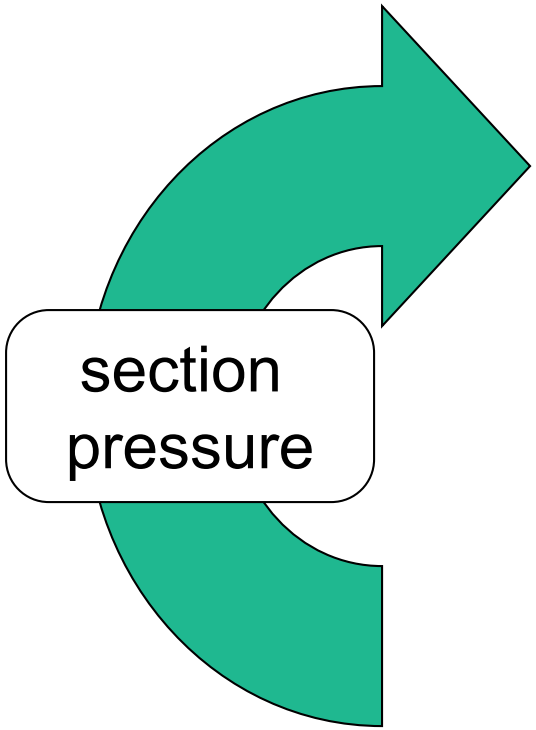




Detail of watercolor by
George Richmond, 1840.
Darwin Museum at Down House

How and why can you select so easily ?

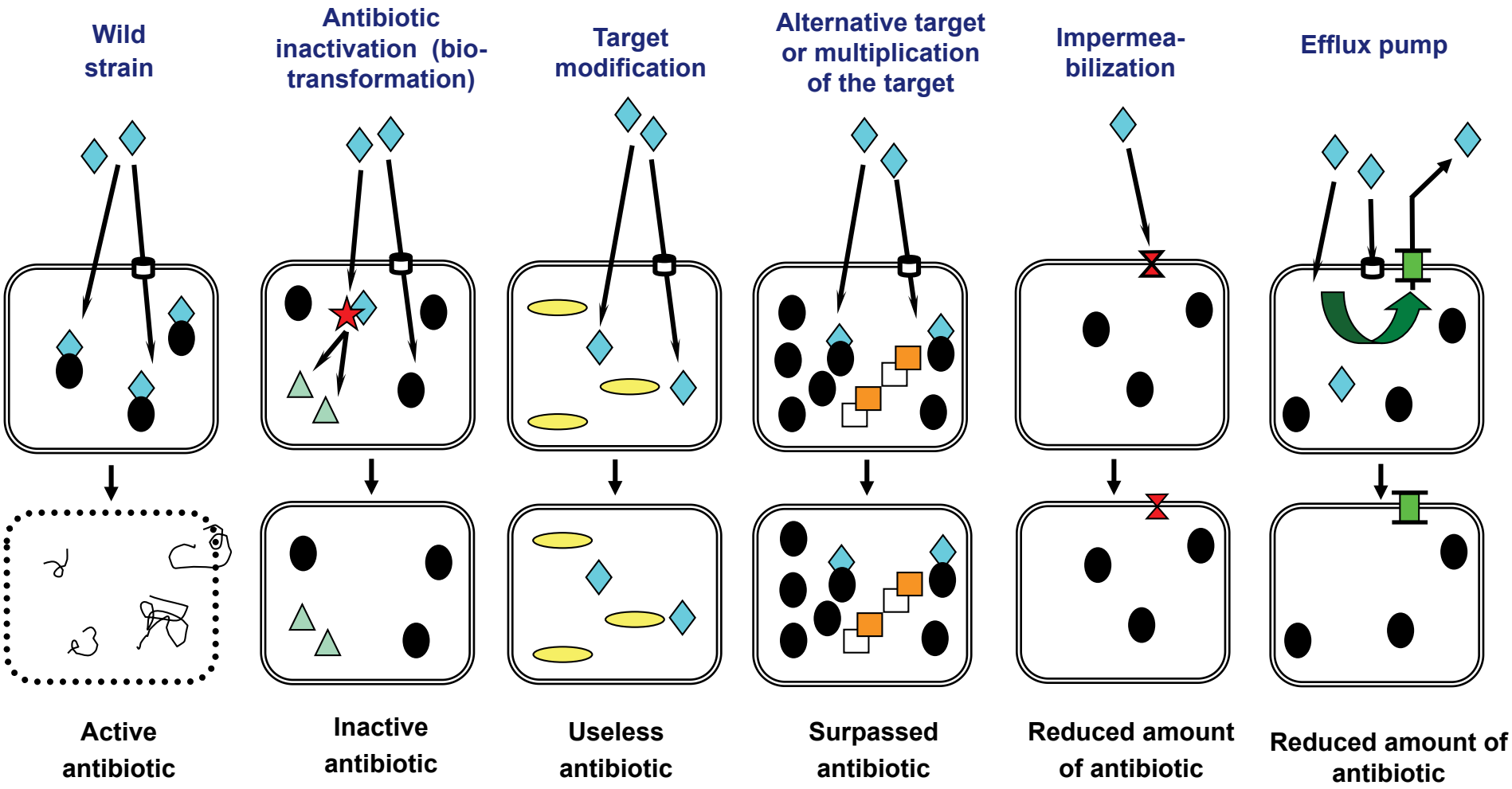
A simple application of Darwin's principle…
to a highly plastic material…



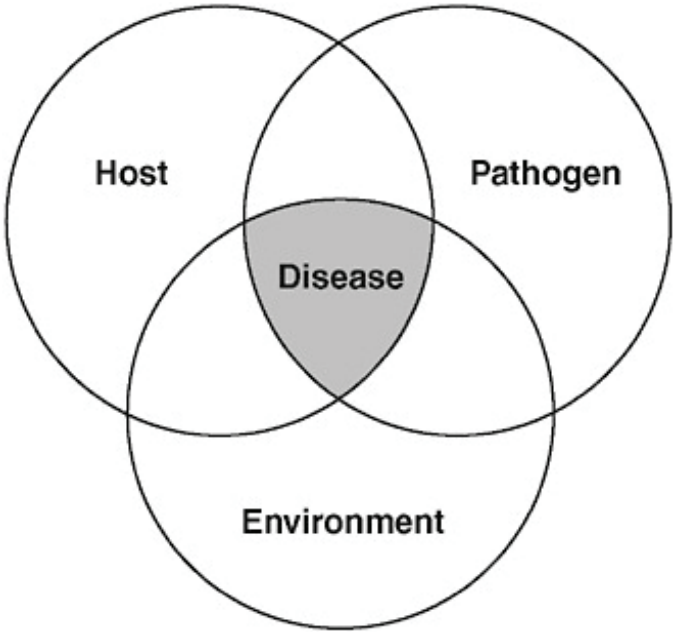
- an infectious focus typicaly contains more than 10^6 - 10^9 organisms
- most bacteria multiply VERY quickly (20 min…) and do mistake …
- they are not innocent or useless mistakes

fast selection of the fittest !

Antibiotic resistance: short overview of main molecular mechanisms



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)

A difficult situation with COPD in Belgium…

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

International Journal of Antimicrobial Agents 44 (2014) 209–217

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

Characterisation of a collection of *Streptococcus pneumoniae* isolates from patients suffering from acute exacerbations of chronic bronchitis: In vitro susceptibility to antibiotics and biofilm formation in relation to antibiotic efflux and serotypes/serogroups

Nathalie M. Vandevelde[a], Paul M. Tulkens[a,*], Yvan Diaz Iglesias[a], Jan Verhaegen[b], Hector Rodriguez-Villalobos[c], Ivan Philippart[d], Julie Cadrobbi[e], Nathalie Coppens[f], An Boel[g], Kristien Van Vaerenbergh[g], Hugo Francart[h], Raymond Vanhoof[i], Giuseppe Liistro[j], Paul Jordens[k], Jean-Paul d'Odemont[l], Yvan Valcke[m], Franck Verschuren[n], Françoise Van Bambeke[a]

[a] *Pharmacologie cellulaire et moléculaire & Centre de Pharmacie Clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium*
[b] *Laboratorium microbiologie, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium*
[c] *Laboratoire de microbiologie, Cliniques universitaires St Luc, Brussels, Belgium*
[d] *Laboratoire de microbiologie, Centre hospitalier régional Mons-Warquignies, Warquignies, Belgium*
[e] *Laboratoire de microbiologie, Clinique et Maternité Ste Elisabeth, Namur, Belgium*
[f] *Service de pneumologie, Clinique et Maternité Ste Elisabeth, Namur, Belgium*
[g] *Laboratorium microbiologie, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium*
[h] *Laboratorium microbiologie, Algemeen Ziekenhuis Nikolaas, St Niklaas, Belgium*
[i] *Institut Scientifique de Santé Publique, Brussels, Belgium*
[j] *Service de pneumologie, Cliniques universitaires St Luc, Brussels, Belgium*
[k] *Pneumologie, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium*
[l] *Service de pneumologie, Centre hospitalier régional Mons-Warquignies, Warquignies, Belgium*
[m] *Longziekten en allergieën, Algemeen Ziekenhuis Nikolaas, St Niklaas, Belgium*
[n] *Service des Urgences, Cliniques universitaires Saint-Luc, Brussels, Belgium*

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Characterisation of a
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Nathalie M. Vandevelde[a],
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Belgium
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[l] Service de pneumologie, Centre hospitalier ré
[m] Longziekten en allergieën, Algemeen Zieken
[n] Service des Urgences, Cliniques universitaire

Table 3

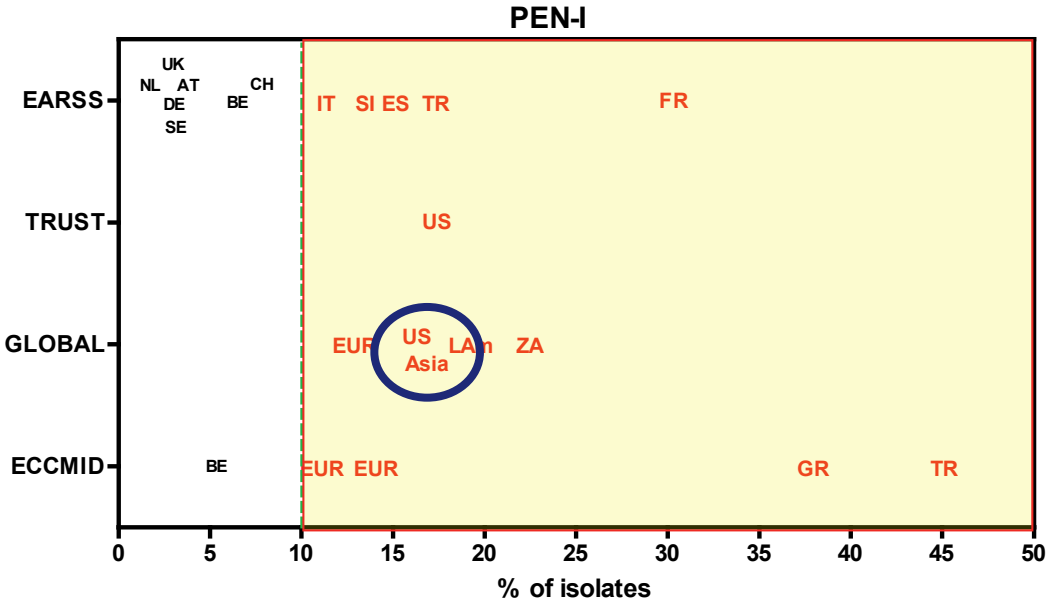
MIC_{50} and MIC_{90} values and percentages of non-susceptible (intermediate and resistant) isolates according to European Committee for Antibiotic Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) interpretive criteria.

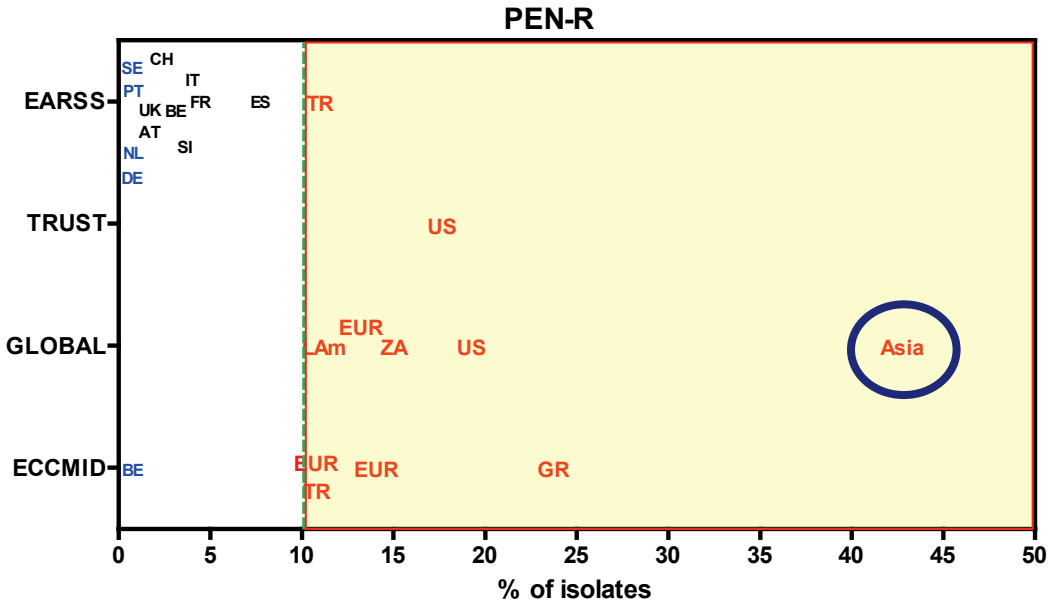
Antibiotic	Strains collection	% Susceptibility according to:			
		EUCAST [20]		CLSI [19]	
		Breakpoint (S/R) (mg/L)	% I/R	Breakpoint (S/R) (mg/L)	% I/R
Amoxicillin	Global	≤0.5/ > 2	8/8	≤2/≥8	1/4
	2006–2008		10/4		0/0
	2010–2013		6/11		2/9.4
Cefuroxime	Global	≤0.25/ > 0.5 [a]	6/13	≤1/≥4[a]	1/7
	2006–2008		6.3/14.6		2/8.4
	2010–2013		5.7/11.3		0/5.7
Clarithromycin	Global	≤0.25/ > 0.5	1/27.7	≤0.25/≥1	7.9/26.7
	2006–2008		0/31.2		0/30.2
	2010–2013		2/24.5		15.1/22.7
Azithromycin	Global	≤0.25/ > 0.5	1/38.6	≤0.5/≥2	6/28.7
	2006–2008		0/31.2		0/31.2
	2010–2013		0/39.6		11.3/26.4
Clindamycin[b]	Global	≤0.5/ > 0.5	0/35.7	NA	NA
	2006–2008		0/27		NA
	2010–2013		0/43.4		NA
Moxifloxacin	Global	≤0.5/ > 0.5	0/8	≤1/≥4	3/0
	2006–2008		0/6.3		2/0
	2010–2013		0/9.4		4/0

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





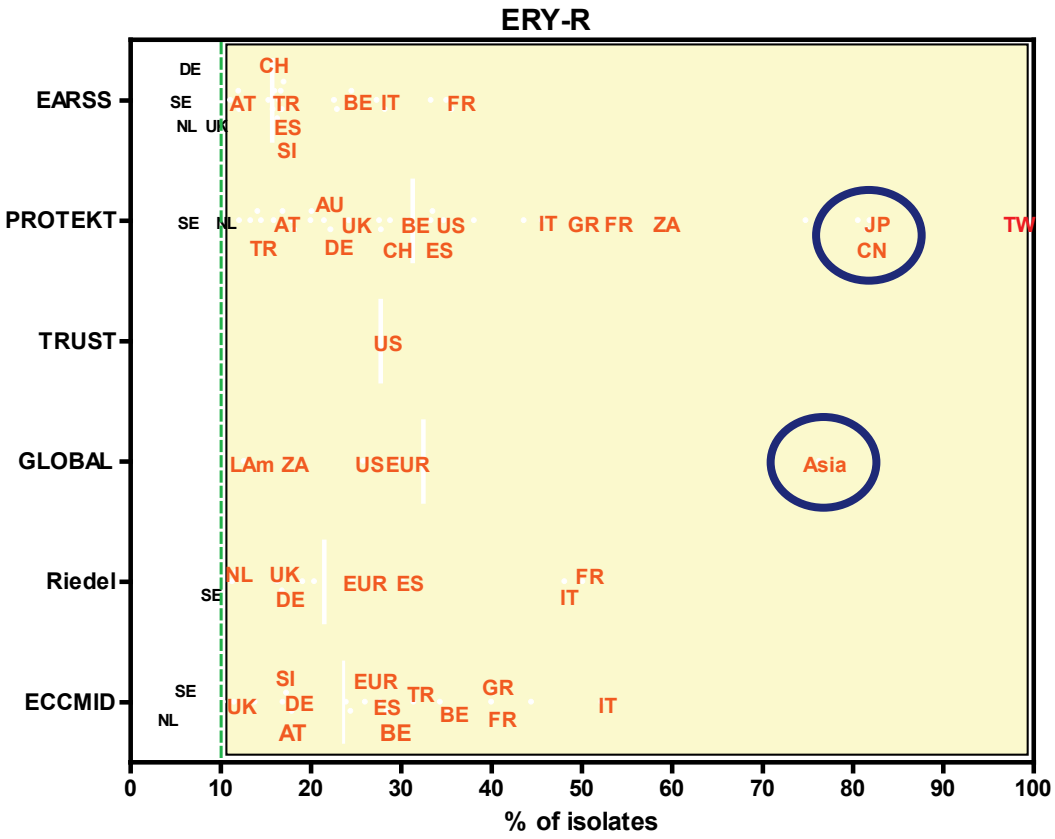
Carbonnelle *et al.*, in preparation

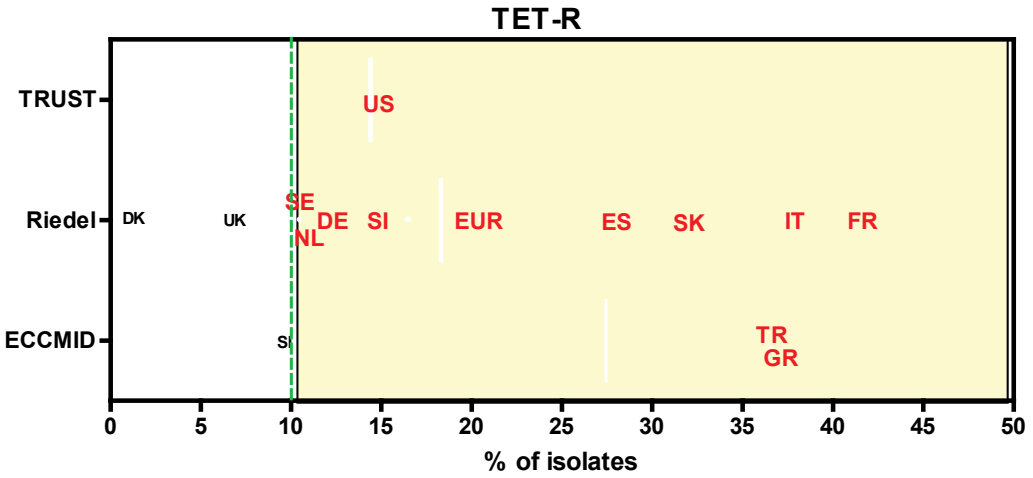
Resistance of *S. pneumoniae* International examples *

*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





Resistance in Cambodia and neighboring countries

OPEN ACCESS Freely available online

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

Resistance in Vietnam: 2: Hospital

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

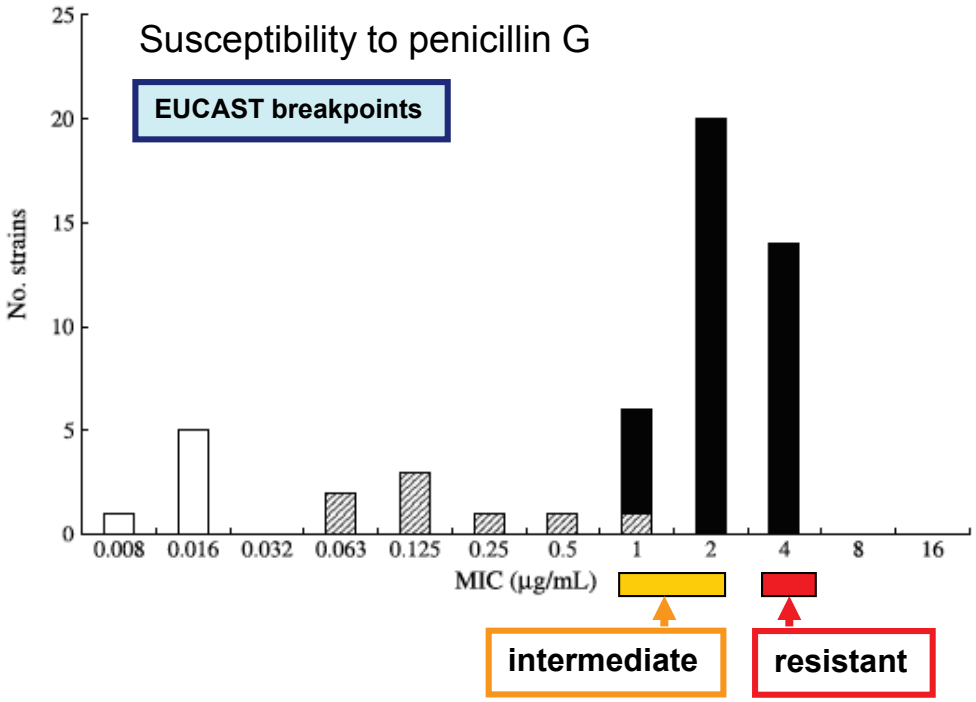
Original Article

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

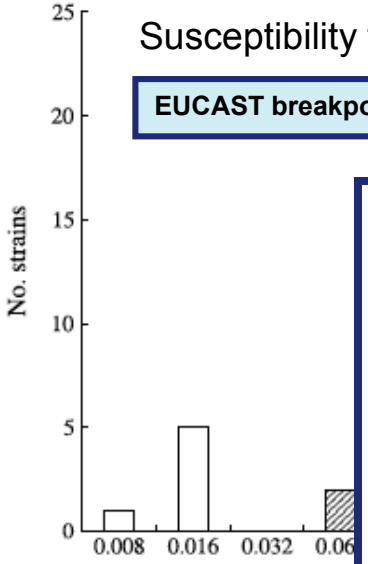


Table 2 Genotype of drug-resistant genes and MIC in 53 strains of *Streptococcus pneumoniae*

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

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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[b] Department of Clinical Laboratory, Peking University People's Hospital, Beijing, China
[c] Beijing Hospital of the Ministry of Health, Beijing, China
[d] Department of Infectious Diseases and Clinical Microbiology and Beijing Institute of Respiratory Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
[e] Department of Clinical Laboratory, The First Hospital of China Medical University, Shenyang, China
[f] The Second Hospital of China Medical University, Shenyang, China
[g] The Second Affiliated Hospital of Medical School of Zhejiang University, Hangzhou, China
[h] The First Affiliated Hospital of Medical School of Zhejiang University, Hangzhou, China
[i] Tongji Hospital, Tongji Medical College of Huazhong University of Science & Technology, Wuhan, China
[j] Guangzhou Institute of Respiratory Disease, Guangzhou, China
[k] Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[l] Zhongshan Hospital, Fudan University, Shanghai, China
[m] Division of Laboratory Medicine, Changi General Hospital, Singapore
[n] Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[o] Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan
[p] Department of Internal Medicine, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan
[q] Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[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).

S. pneumoniae: Indonesian data

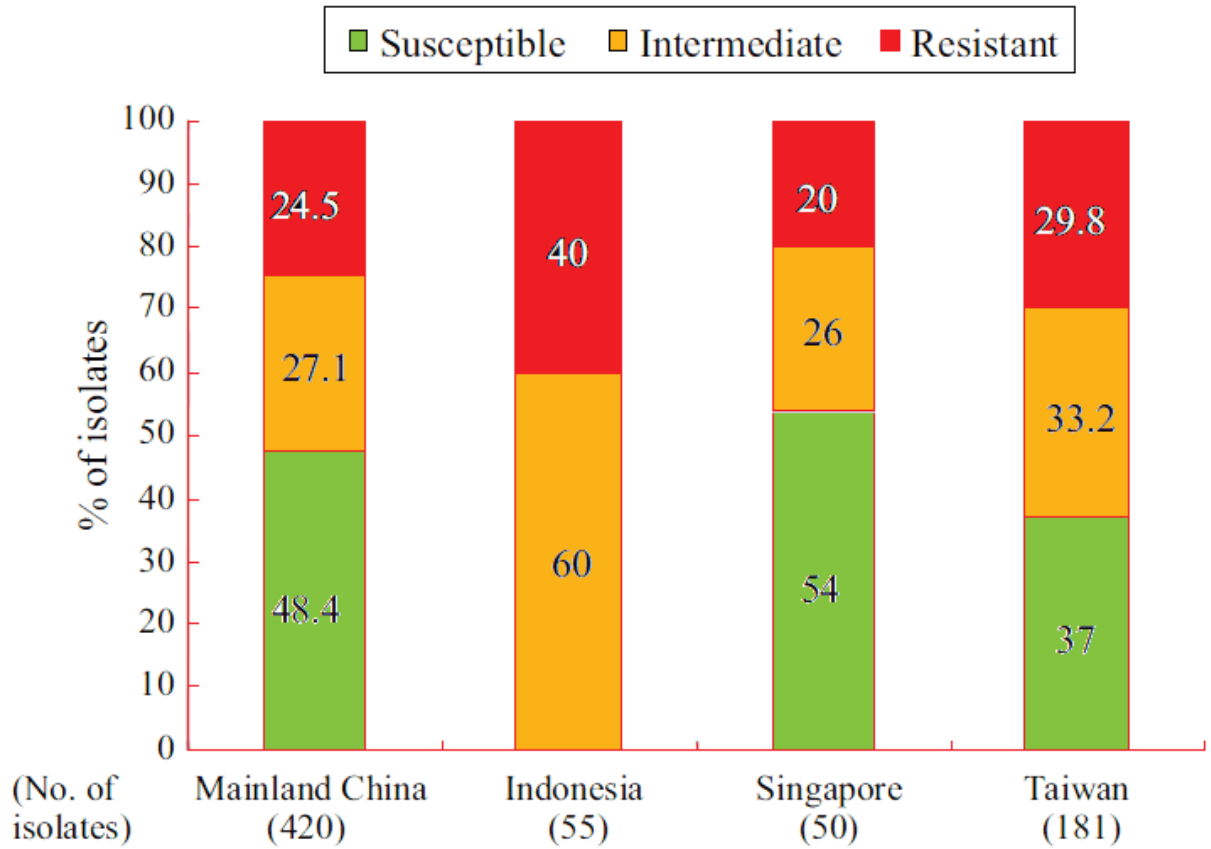


Fig. 1. Distribution of susceptibility of *Streptococcus pneumoniae* isolated from patients in Mainland China, Taiwan, Singapore and Indonesia based on the break-points of oral penicillin V [11].

Resistance in Vietnam Community

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

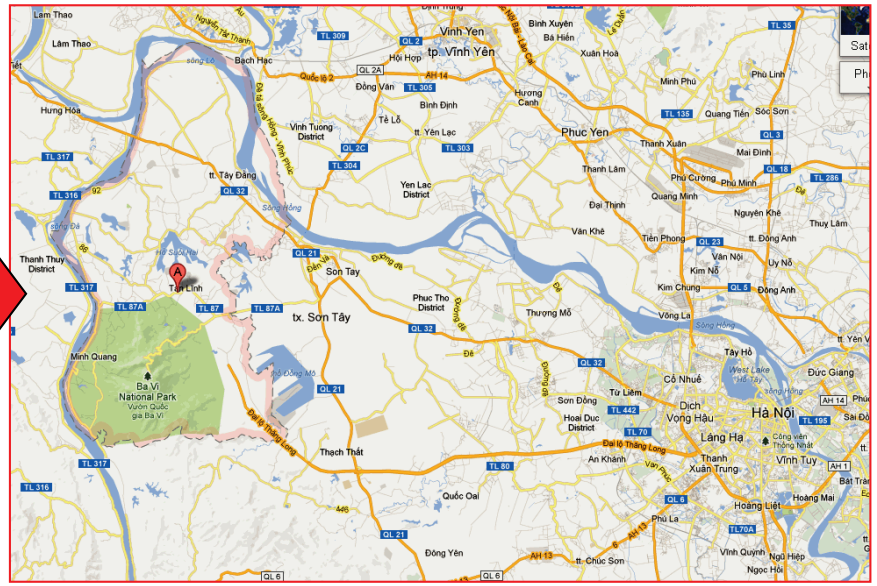
BMC Infectious Diseases

RESEARCH ARTICLE Open Access

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

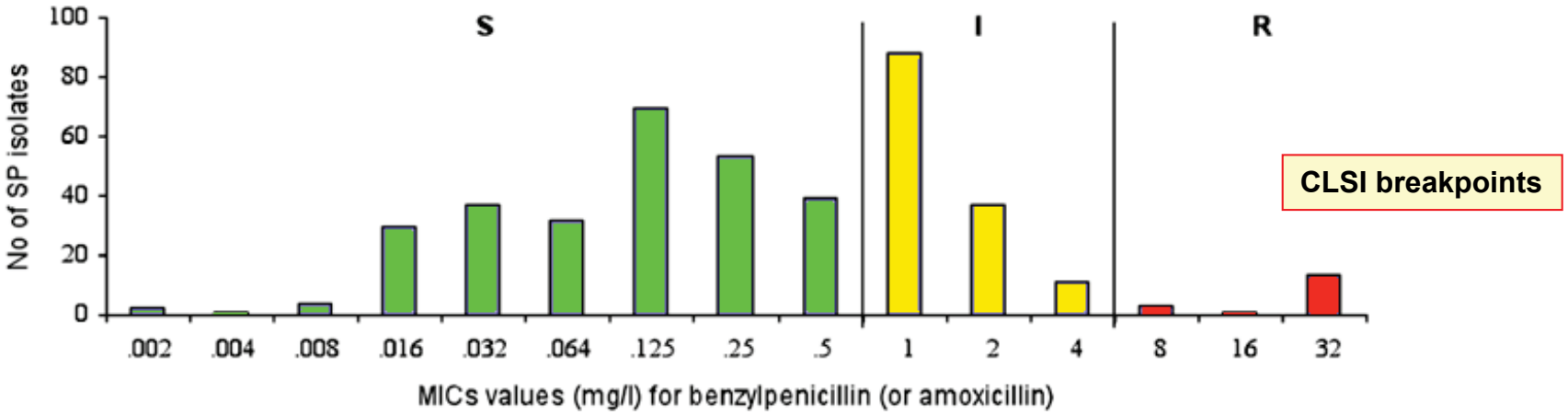
Nguyen Quynh Hoa[1,2*], Nguyen V Trung[3,4], Mattias Larsson[1], Bo Eriksson[5], Ho D Phuc[6], Nguyen TK Chuc[7], Cecilia Stalsby Lundborg[1]

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 …

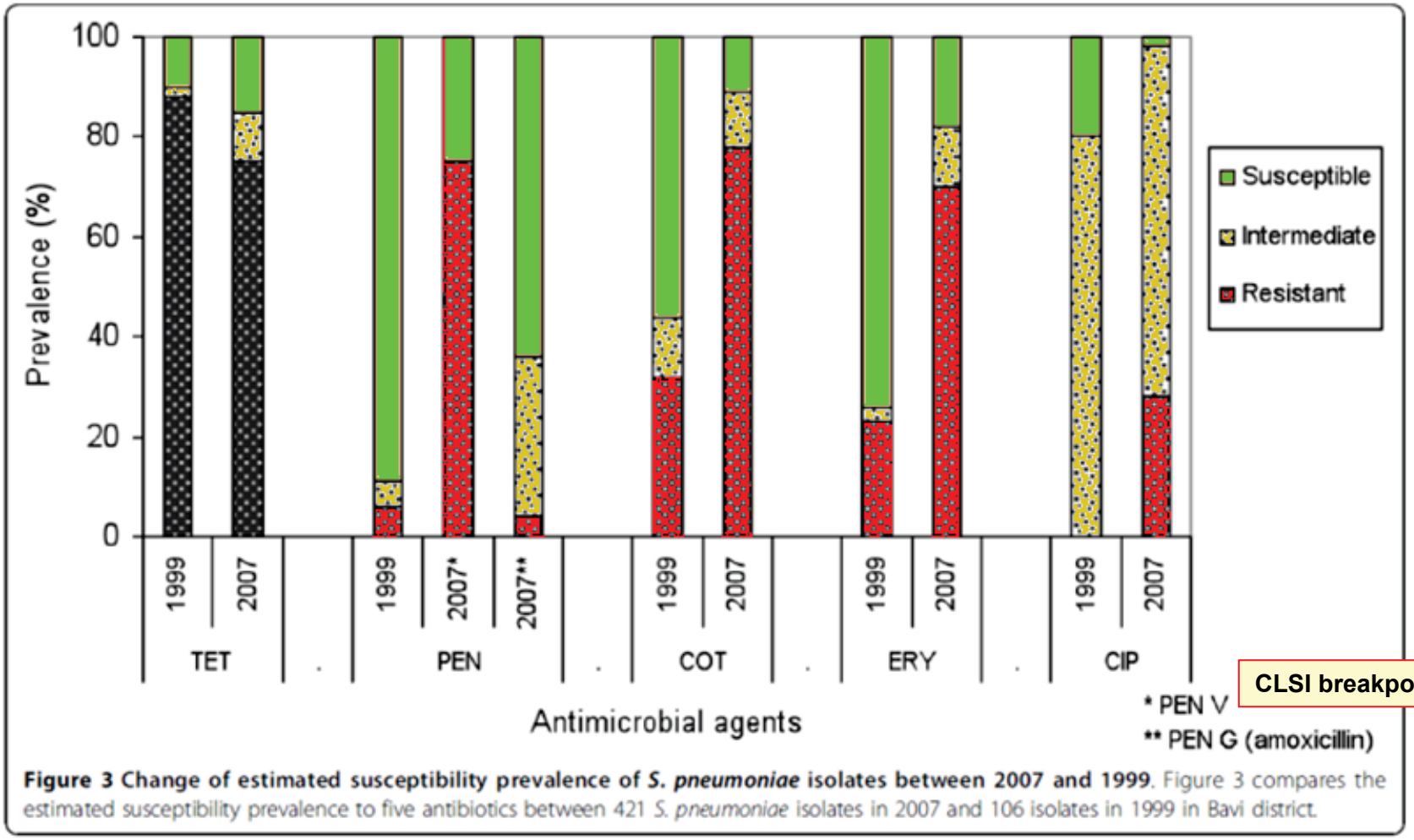


Figure 3 Change of estimated susceptibility prevalence of *S. pneumoniae* isolates between 2007 and 1999. Figure 3 compares the estimated susceptibility prevalence to five antibiotics between 421 *S. pneumoniae* isolates in 2007 and 106 isolates in 1999 in Bavi district.

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

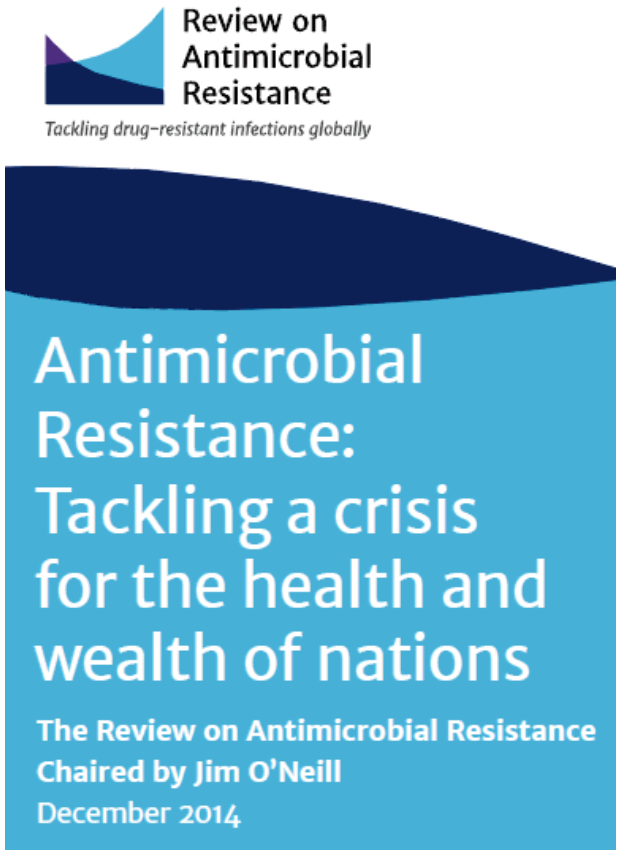
- Countries (and Regions) should know THEIR resistance patterns!

The message: make and use surveys

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

Nguyen Phong Hong (7) of Vietnam and Dinan Javier (9) of Indonesia compete for the ball during the AFF U19 Cup Final match between Indonesia and Vietnam at Gelora Delta Stadium on September 22, 2013 in Sidoarjo, East Java, Indonesia.

What are the risks ?



http://amr-review.org/

What are the risks ?

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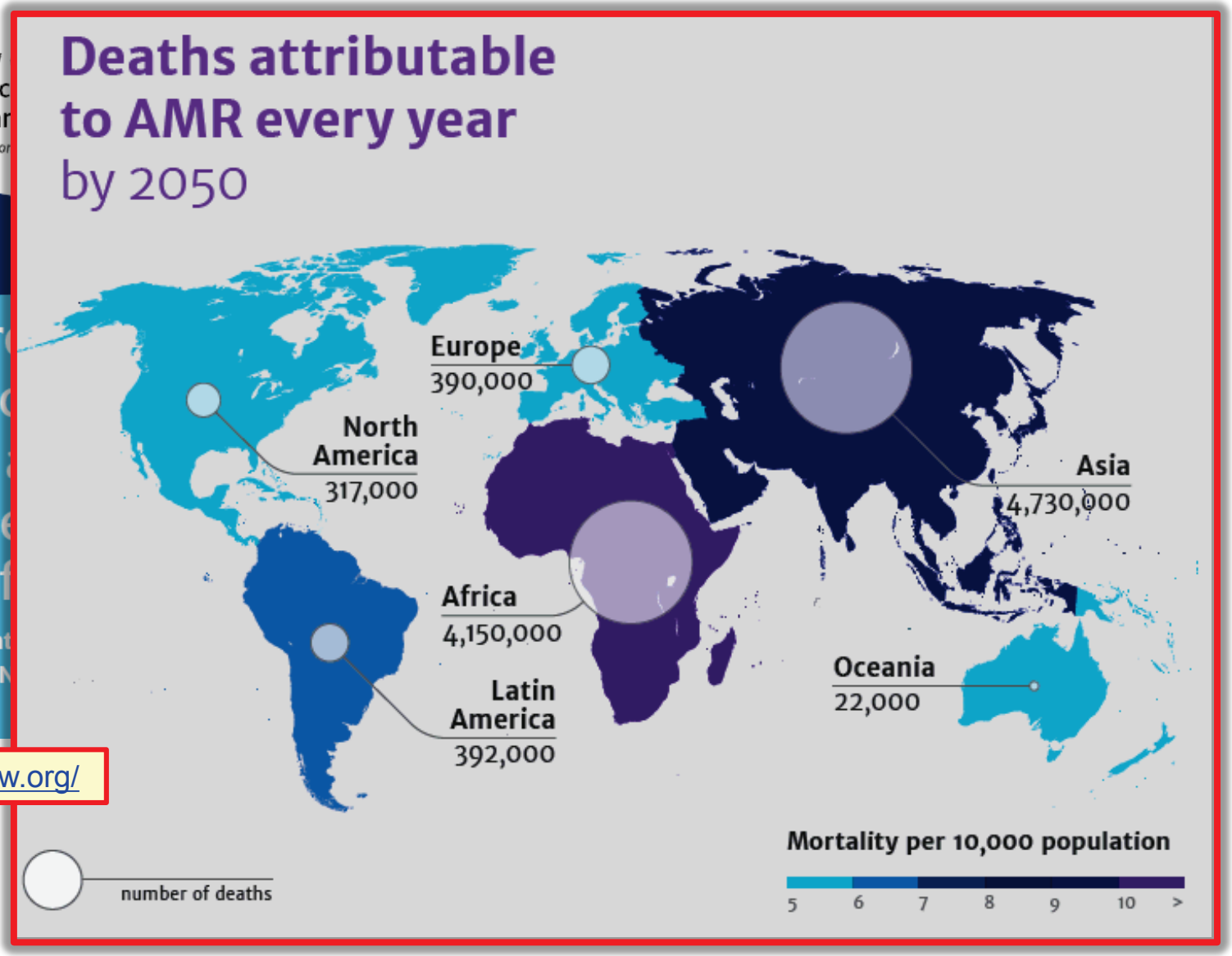
The Review on Ant
Chaired by Jim O'N
December 2014

http://amr-review.org/



AMR: antimicrobial resistance

Conclusions and Recommendations (1 of 3)

- Not all RTI are bacterial but viral infections predispose to colonization and infections by true bacterial pathogens…
- This explains why prescribers believe they need to offer antibiotic coverage in all cases…

http://careinfo.in/2015/05/how-to-fight-side-effects-of-antibiotics/

But all antibiotics have side effects …

http://www.angelreyesblog.com/2012/09/articles/in-the-news/certain-antibiotics-shown-to-have-serious-side-effects/

Conclusions and Recommendations (2 of 3)

Therefore, any prescription should assess…

- the **risk/benefit balance** for **individual patients**
- the **perturbation of microbiome** that may affect both **individual patients** (facilitation of the infection) and the **community** (epidemics)
- The current and foreseeable **resistance to antibiotics** that will **affect all present and future patients**

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

Conclusions and Recommendations (3 of 3)

- The only real solution would be to **use much less antibiotics** (there is compelling evidence that increase in antibiotic use is associated with an increase in the percentage of resistant strains)

ANTIBIOTIC GUARDIAN

EUROPEAN ANTIBIOTIC AWARENESS DAY

A European Health Initiative

This is why strategies to prevent infections and alternative method of controlling established infections are badly needed…

Please, ask questions…

I'll do my best

Back-up

"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 hidden risk of therapy (in our hospitals …)

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

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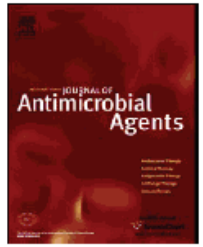

In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

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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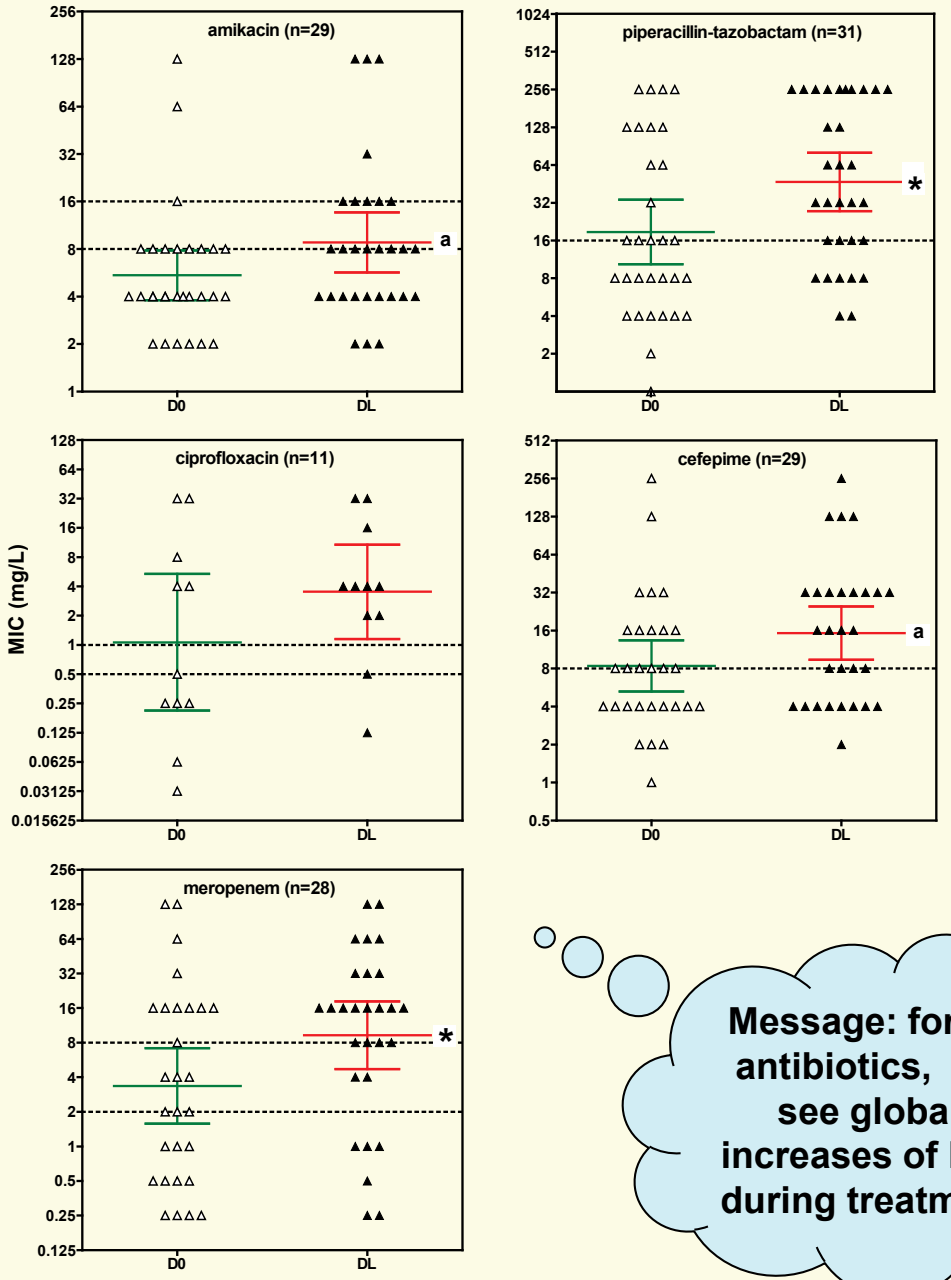
Do you remain effective while treating ?

- 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])
[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
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Nguyen Thi [illegible]hu H[illegible]ai *et al.* (post-doc a[illegible] LDRI)
presented at the 8t[illegible] ISAAR, [illegible]eou[illegible] Korea, 8 April 201[illegible] p[illegible]ogress
[illegible] Chi Minh

sub-MIC concentrations select for resistance !

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

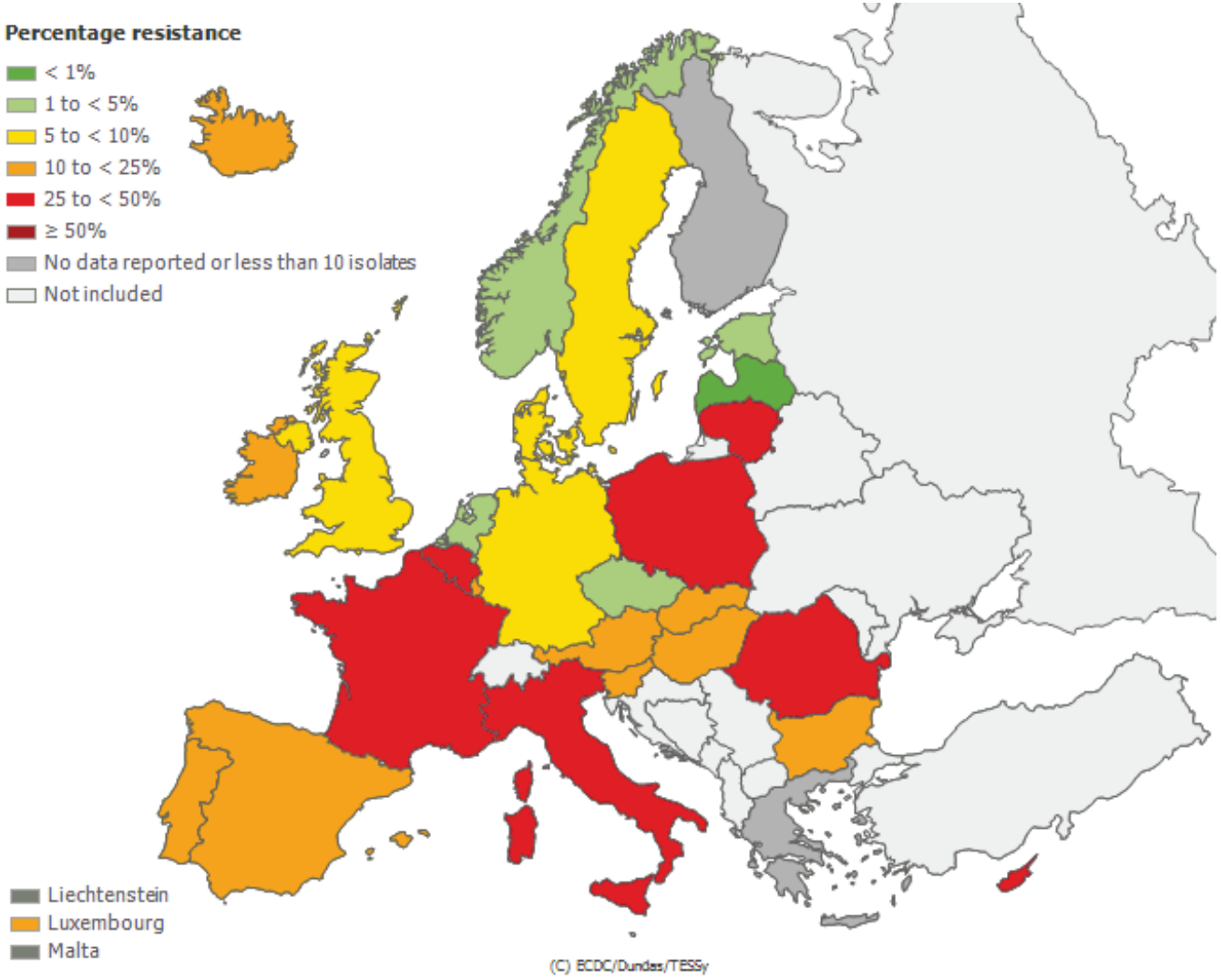
Main resistance mechanisms of bacteria of importance in Respiratory Tract Infections and how to fight them

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: European surveys of resistance to macrolides



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

S. pneumoniae: example in Belgium for CAP

Contents lists available at SciVerse ScienceDirect

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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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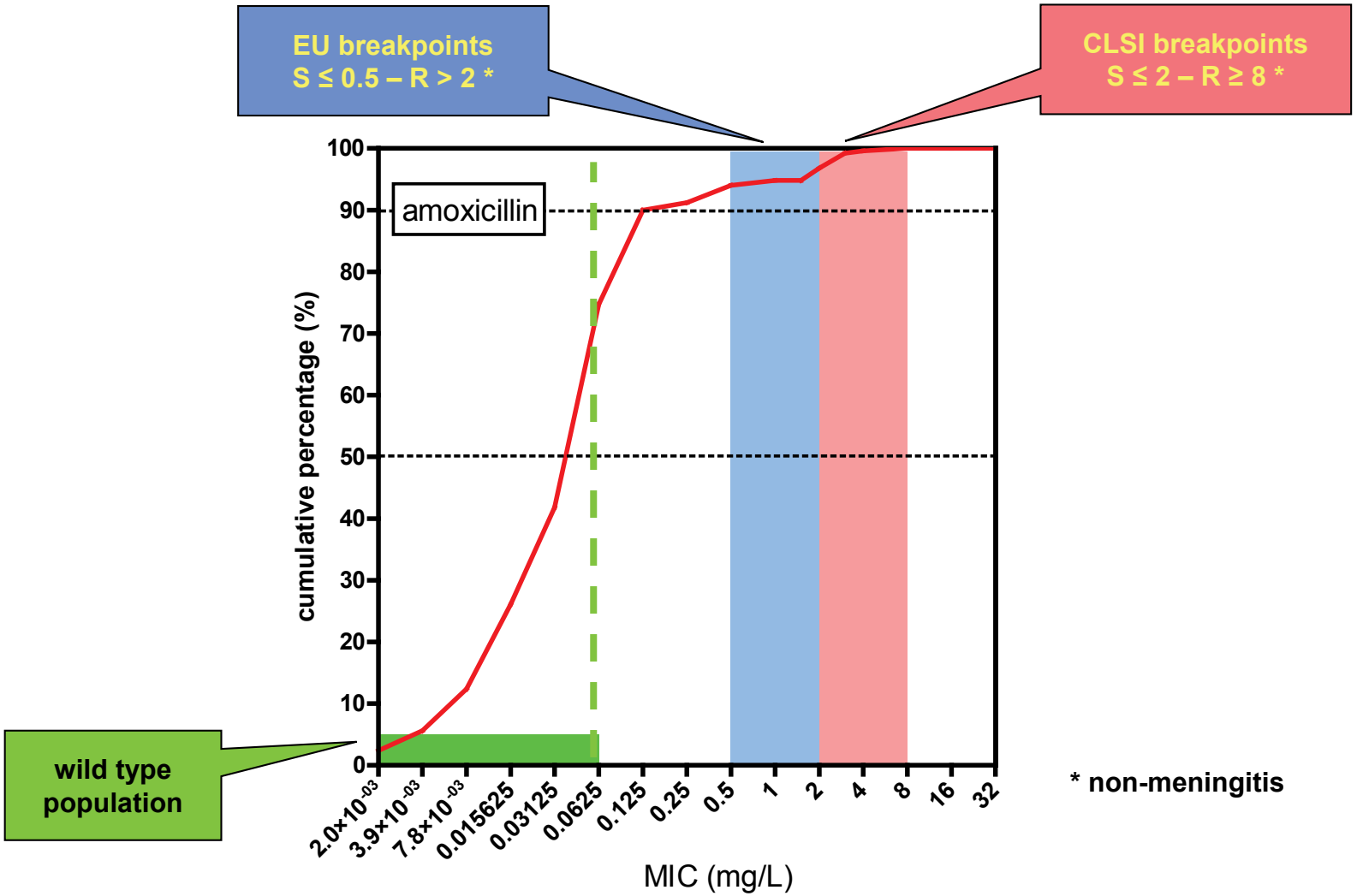
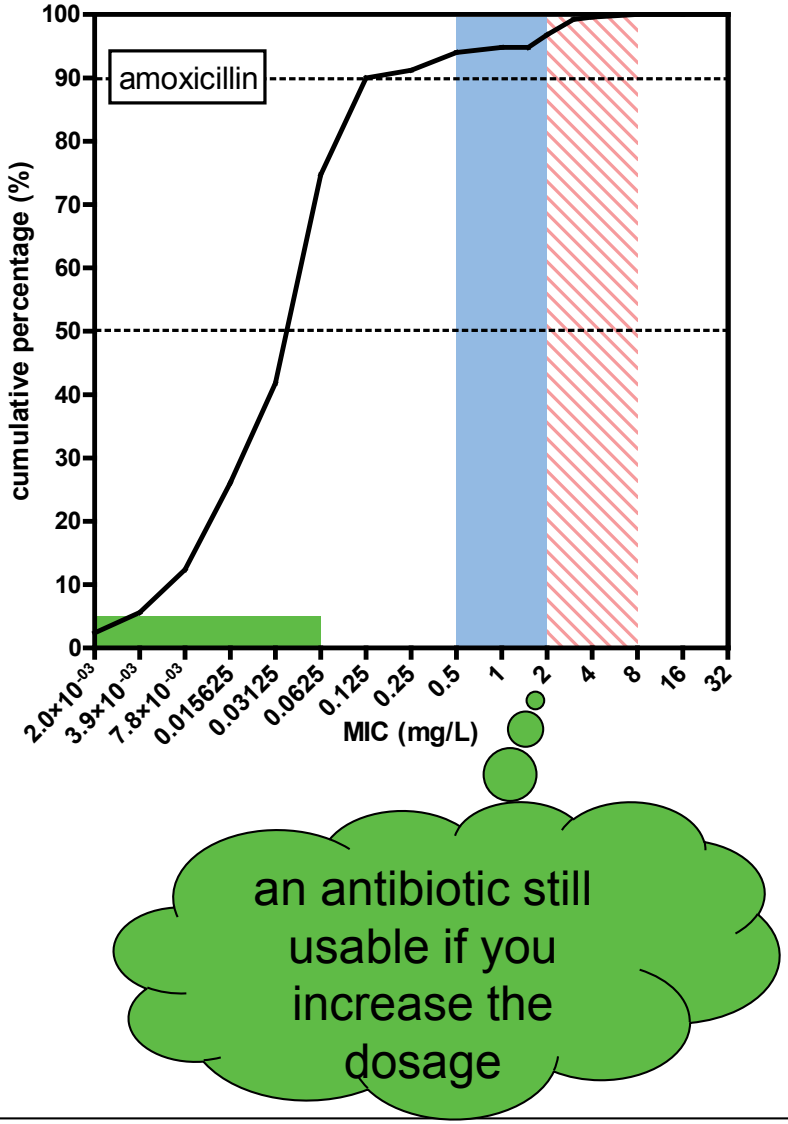
[j] *Laboratoire de microbiologie, CHU Mont-Godinne, Yvoir, Belgium*

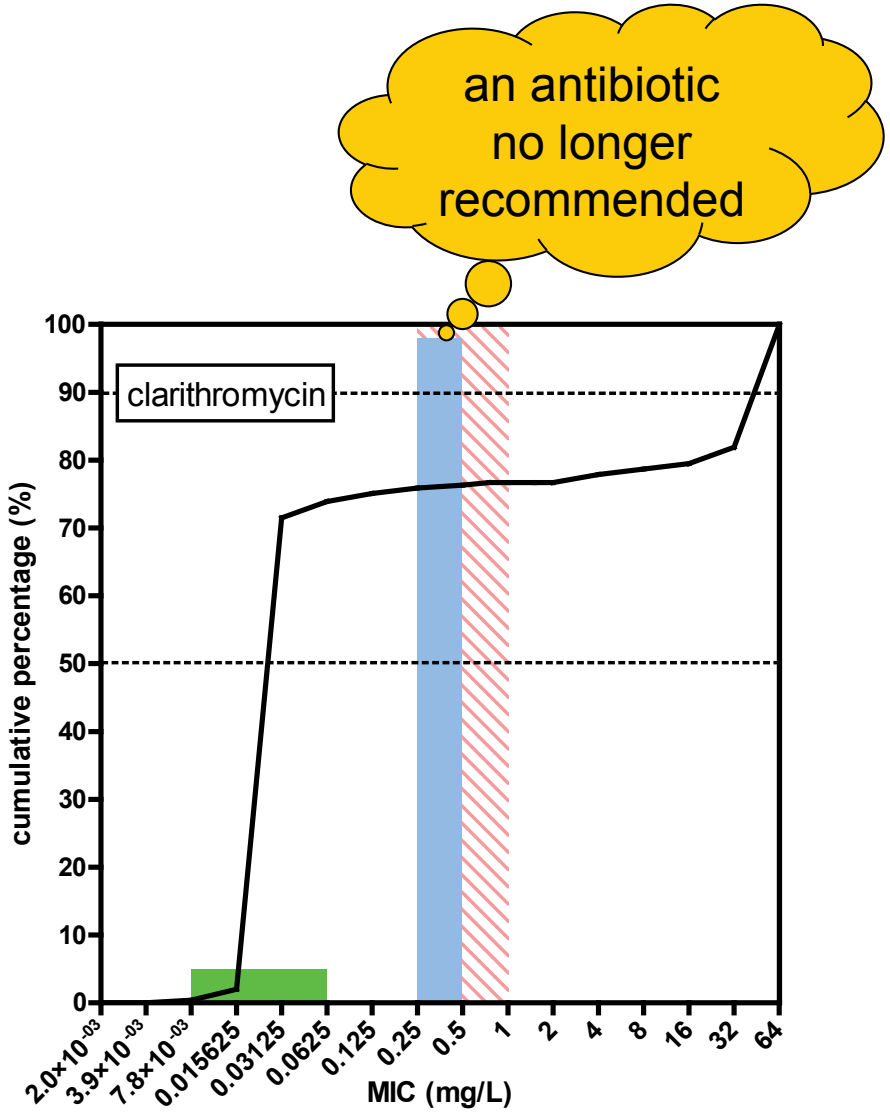
S. pneumoniae: an example in Belgium for CAP



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

S. pneumoniae: how to make antibiotic policy





Very 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 in less severe indications: 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)