呼吸道感染全球抗生素耐药性

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OM Pharma

中国大师班

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我们是否面对一个问题？

Obituary

J.-M. Ghuysen

此人发现了青霉素的作用模式

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

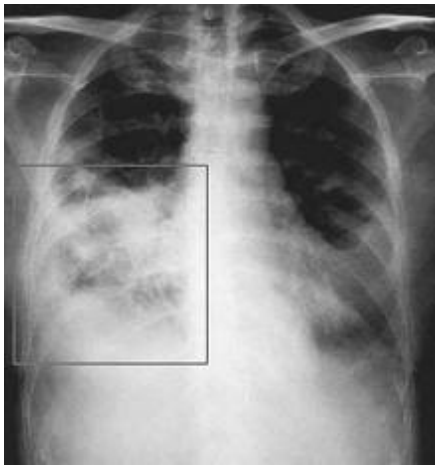
Service de Microbiologie, Faculté de Médecine, Institut de Botanique, Université de Liège, 4000 Sart Tilman, Liège, Belgium

却死于侵入性肺炎球菌感染.....

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

我们是否面对一个问题？

- 社区获得性肺炎：
  - 仍然是急性死亡的一个主要原因（第3至第7位）；
  - 死亡率介乎<2%至30%之间，实际死亡率更多很大程度上取决于并存疾病、宿主防御的状态和年龄；
  - *肺炎链球菌*是最常见的病原体，但在特定的情况中，其他细菌可能是至关重要的（致病微生物仍然存在，但是在30%至50%的情况下未被确认）。



CAP：社区获得性肺炎

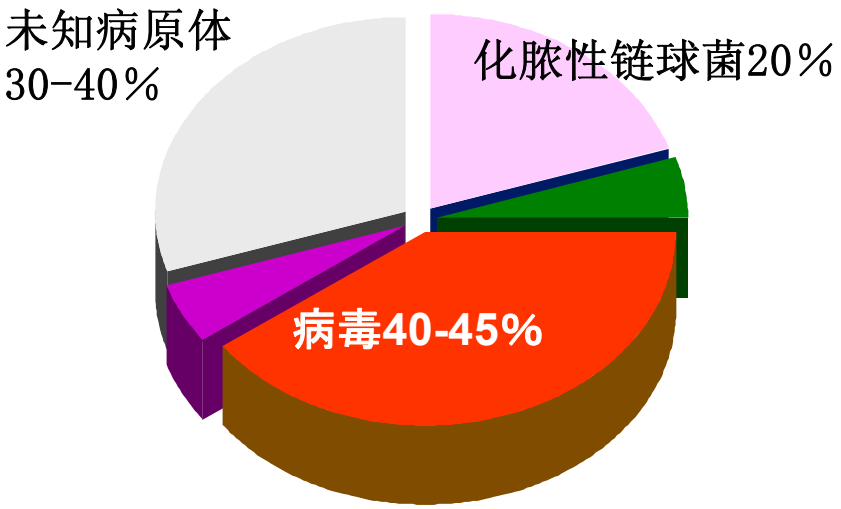
演讲内容和目标

- 疾病和敌人
  - 上呼吸道感染
  - 下呼吸道感染
- 耐药性
  - 一般概念（抗性基因、选择数据库、不当使用）
  - 主要细菌的主要机制
- 流行病学
  - 主要原则和要求
  - 肺炎链球菌举例
  - 折点
  - 绿脓杆菌举例

疾病和敌人

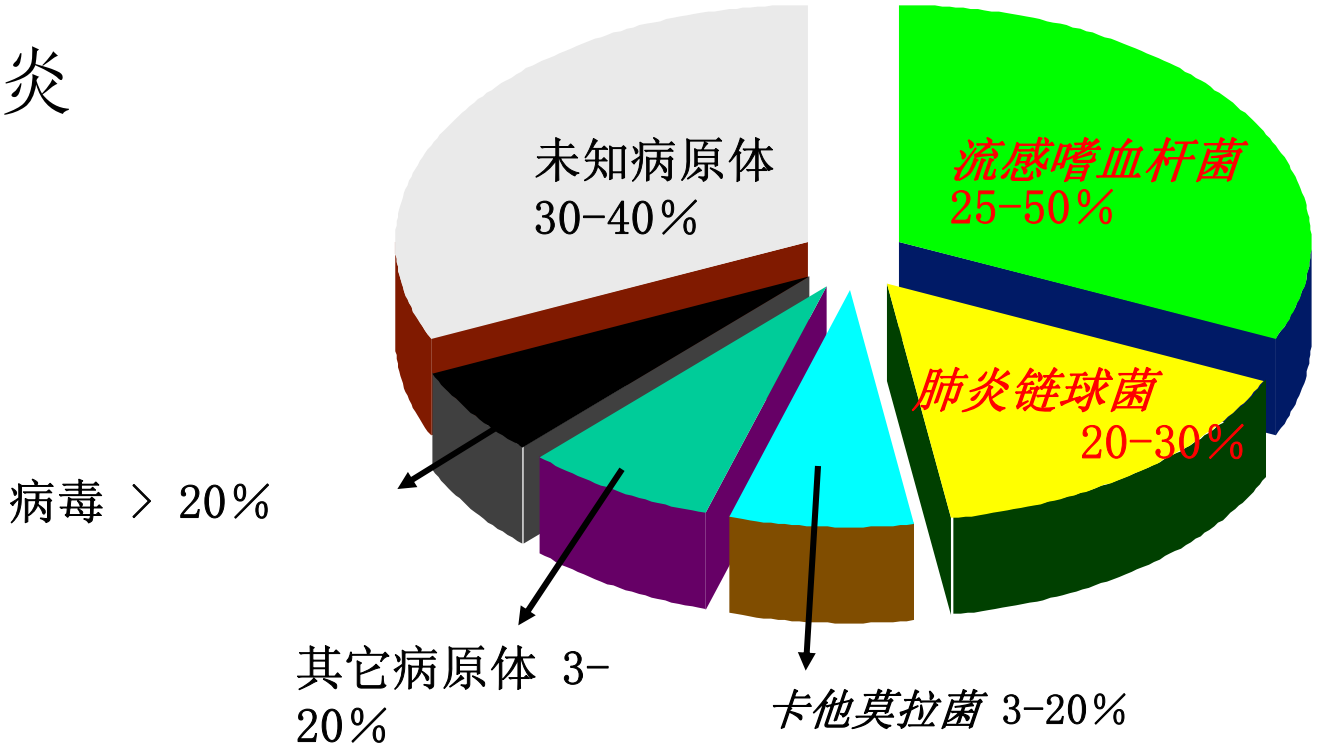
上呼吸道感染的主要病原体

1. 咽炎



上呼吸道感染的主要病原体

2. 耳炎

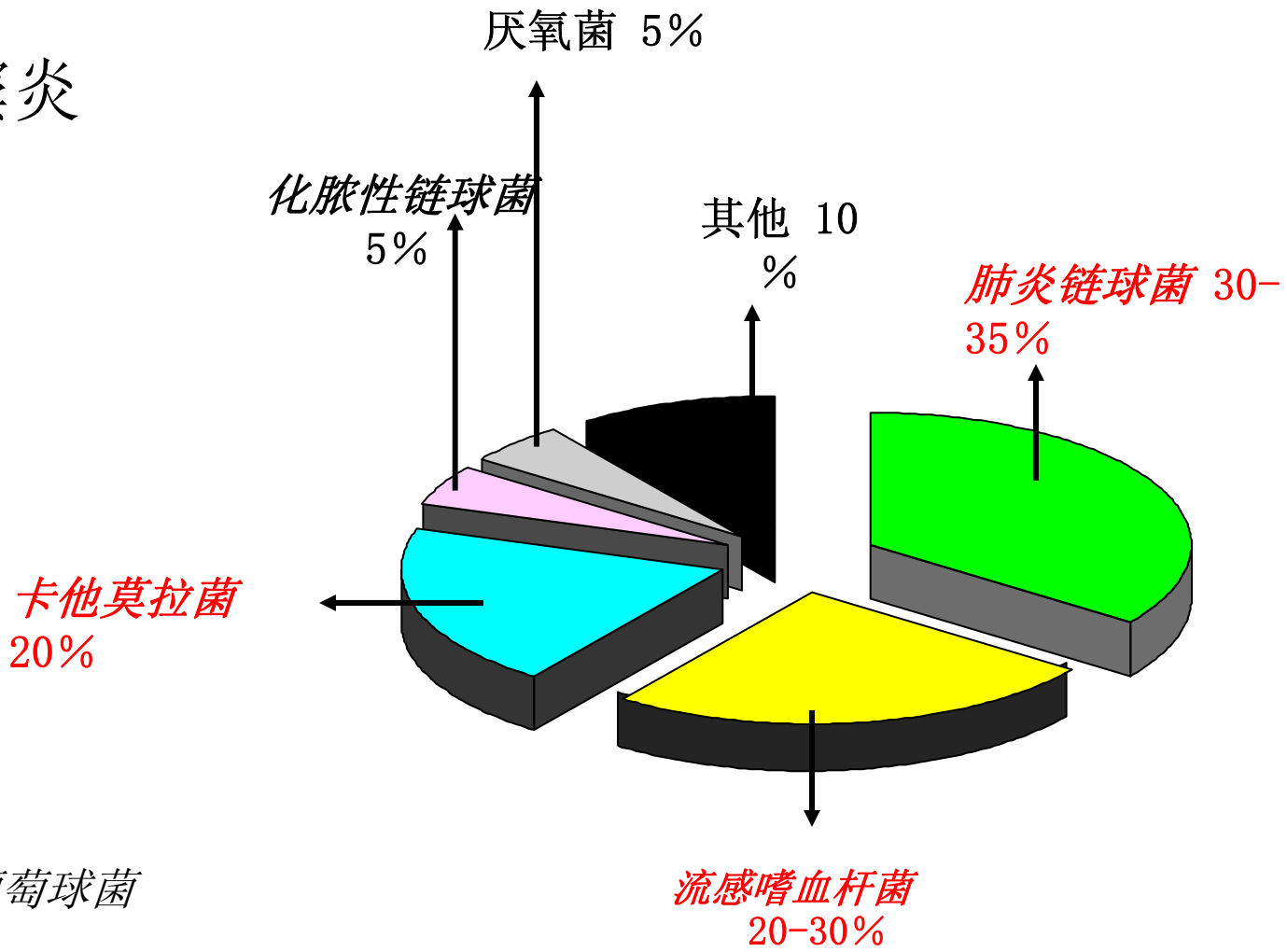


但还有：

- *大肠杆菌、假单胞菌*
- *支原体、衣原体*

上呼吸道感染的主要病原体

3. 鼻窦炎



但还有:

- *金黄色葡萄球菌*

下呼吸道感染的主要病原体

1. 慢性阻塞性肺病（COPD）

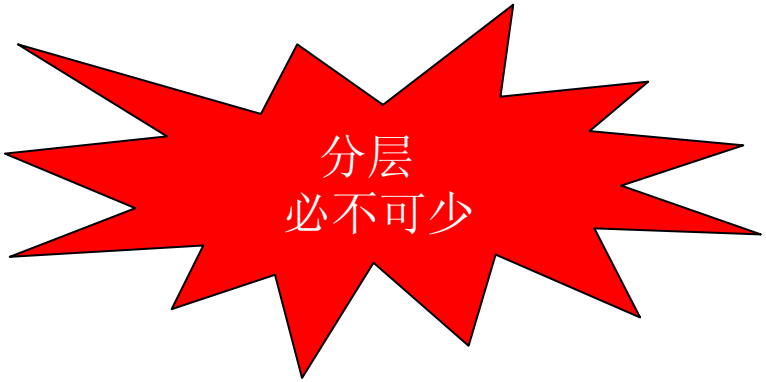
- **急性发作**
  （频度不同 — 一年2次到多次）
  - *流感嗜血杆菌*
  - *卡他莫拉菌*
  - *肺炎链球菌*

- **如果合并其他疾病**（糖尿病、心功能不全.....）
  - *肺炎克雷伯氏菌*
  - *铜绿假单胞菌*
  - 其他革兰氏阴性菌

下呼吸道感染的主要病原体

2. 肺炎

- 社区获得性（CAP）
  - 无危险因素的年轻成人患者
  - 儿童和老人
  - 共存疾病和疾病严重程度
- 医疗保健相关
  - 护理院
  - 医院
- 免疫功能低下病人
  - 无脾
  - 艾滋病病毒感染
  - 抗癌治疗



社区获得性肺炎的主要病原体（成人）

病原体	频率(%)
未确定病原体	**49.8**
肺炎链球菌	**19.3**
病毒	11.7
肺炎支原体	11.1
肺炎衣原体	8.0
流感嗜血杆菌	3.3
军团菌	1.9
其他生物	1.6
鹦鹉热衣原体	1.5
贝氏柯克斯体	0.9
卡他莫拉菌	0.5
革兰氏阴性肠道细菌	0.4
金黄色葡萄球菌	0.2

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

在亚洲，最新的报告数字（%）有所不同

- 2.2（中国）
- 1至23（台湾）
- 1.3至20（菲律宾）
- 3.1至5.5（马来西亚）
- 12（韩国）
- 20.6至23.1（泰国）
- 35.8（印度）

Jae-Hoon Songa等Intern.
J.Antimicrob.Ag.38 (2011) 108 - 117

社区获得性肺炎：年龄、疾病的严重程度和环境对细菌类型的重要性

病原体	频率(%)
未确定病原体	**49.8**
肺炎链球菌	**19.3**
病毒	11.7
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其他生物	1.6
鹦鹉热衣原体	1.5
贝氏柯克斯体	0.9
卡他莫拉菌	0.5
革兰氏阴性肠道细菌	0.4
金黄色葡萄球菌	0.2

- □ 在年轻人中
- □在严重病例中
- □**在严重病例和合并疾病中**
- □在当地环境中（美国）

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

医疗保健相关性肺炎

之前所有各项加上：

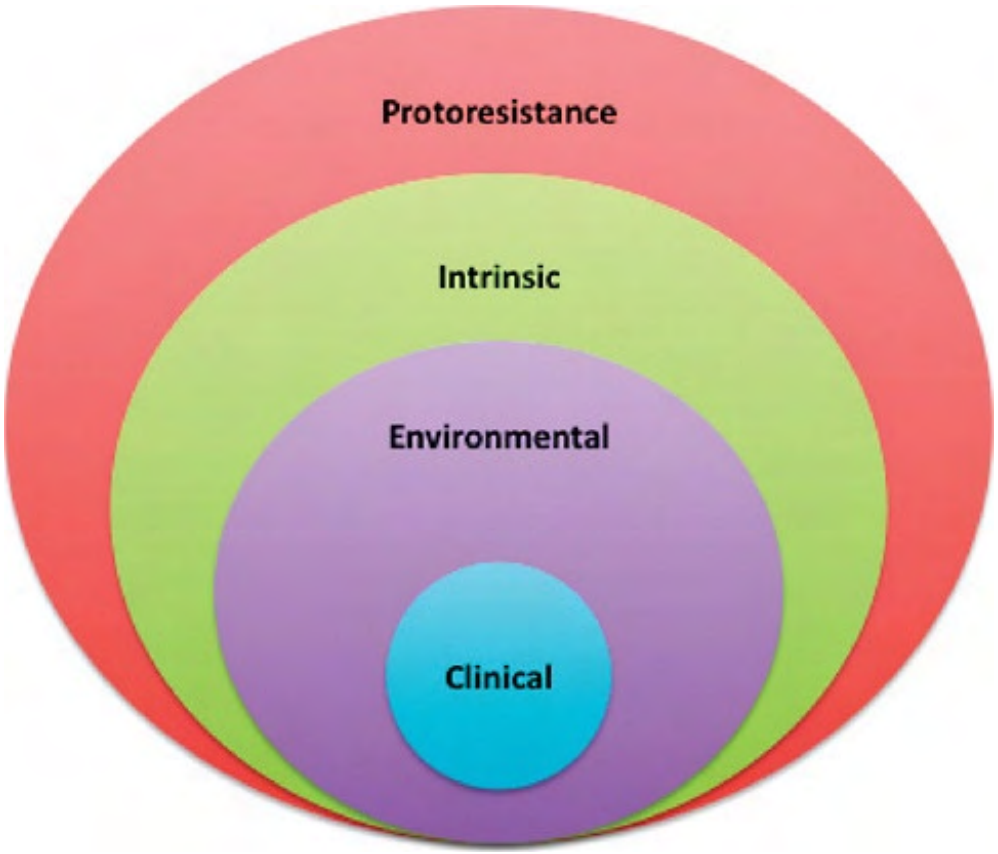
- 革兰氏阳性
  - 肺炎链球菌（最常见为多重抗药性）
  - 耐甲氧西林*葡萄球菌*（包括*金黄色葡萄球菌*）
  - 肠球菌
- 革兰氏阴性
  - 肠杆菌（*大肠杆菌*、*肺炎克雷伯菌*）
  - *鲍曼不动杆菌*
  - 铜绿假单胞菌
- 厌氧菌

耐药性

耐药性：一般概念

- 耐药机制很普遍，在临床使用抗生素时代出现之前往往已经存在。
  - Ø 抗性基因的概念
- 耐药性与抗生素的使用之间存在着固有的联系
  - Ø 选择数据库的概念
    - v 无抗生素□无选择
    - v 以非高效的方式大量使用抗生素□大量选用
- 耐药性“储存宿主”是最经常检测不到的
  - Ø 动物储存宿主
  - Ø 共生菌
  - Ø 定植

抗性基因.....



抗生素抗性基因

- 造成抗生素耐药性的所有基因及其产物
- 高度冗余和相互关联的系统
- 临床耐药性不能充分代表细菌的耐药性
- 既有的生化机制（原型抗性基因）作为深层的前体储存库，可被共同选入和演化

抗生素耐药性：对全球健康和新干预策略的影响：研讨会总结
http://www.nap.edu/openbook.php?record_id=12925

“父亲耐药基因”：
氨基糖苷类初始举例

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†

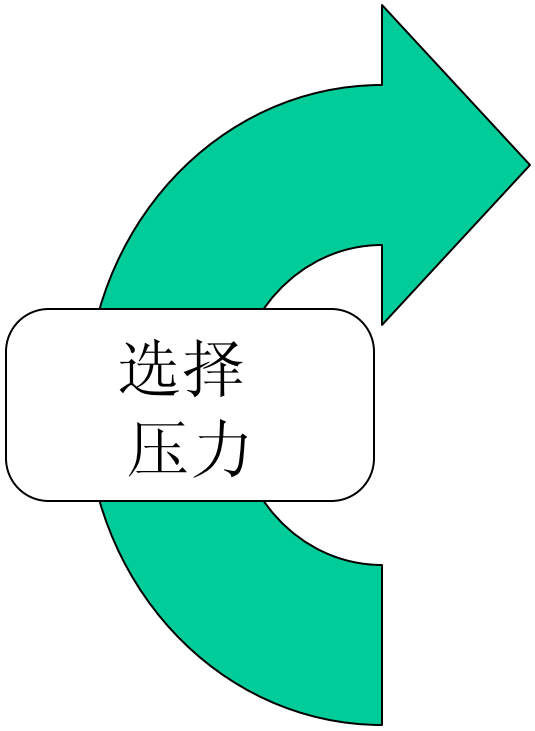
Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin—Madison, Madison, Wis. 53706

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.

选择数据库

达尔文原则的简单应用.....



基因

↓

酶/核蛋白

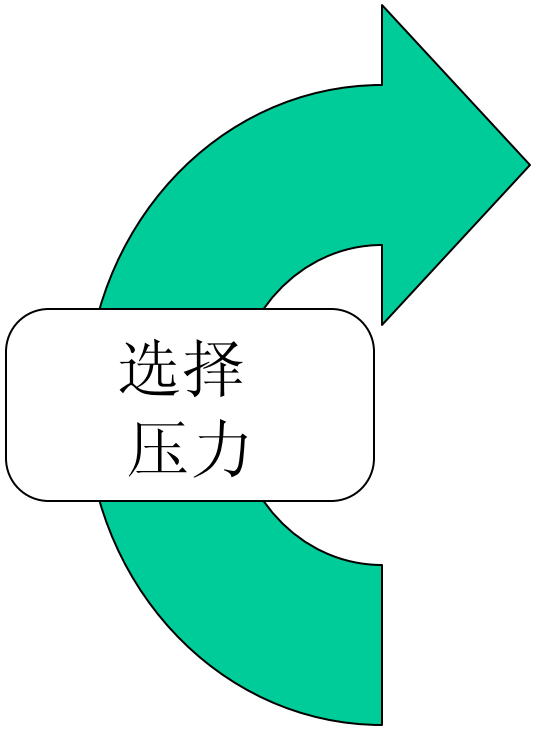
↓

功能

水彩画细节
George Richmond，1840年。
达尔文故居(Down House)达尔文博物馆

你如何容易的做出选择？并为什么？

将达尔文原则简单应用.....
于一种高塑性的材料.....



- 一个传染发源地通常包括超过10^6 - 10^9个生物
- 大多数细菌的繁殖速度非常快（20分钟）而且会出现错误.....
- 但这些不是无辜或无用的错误

适者生存的快捷选择方式！

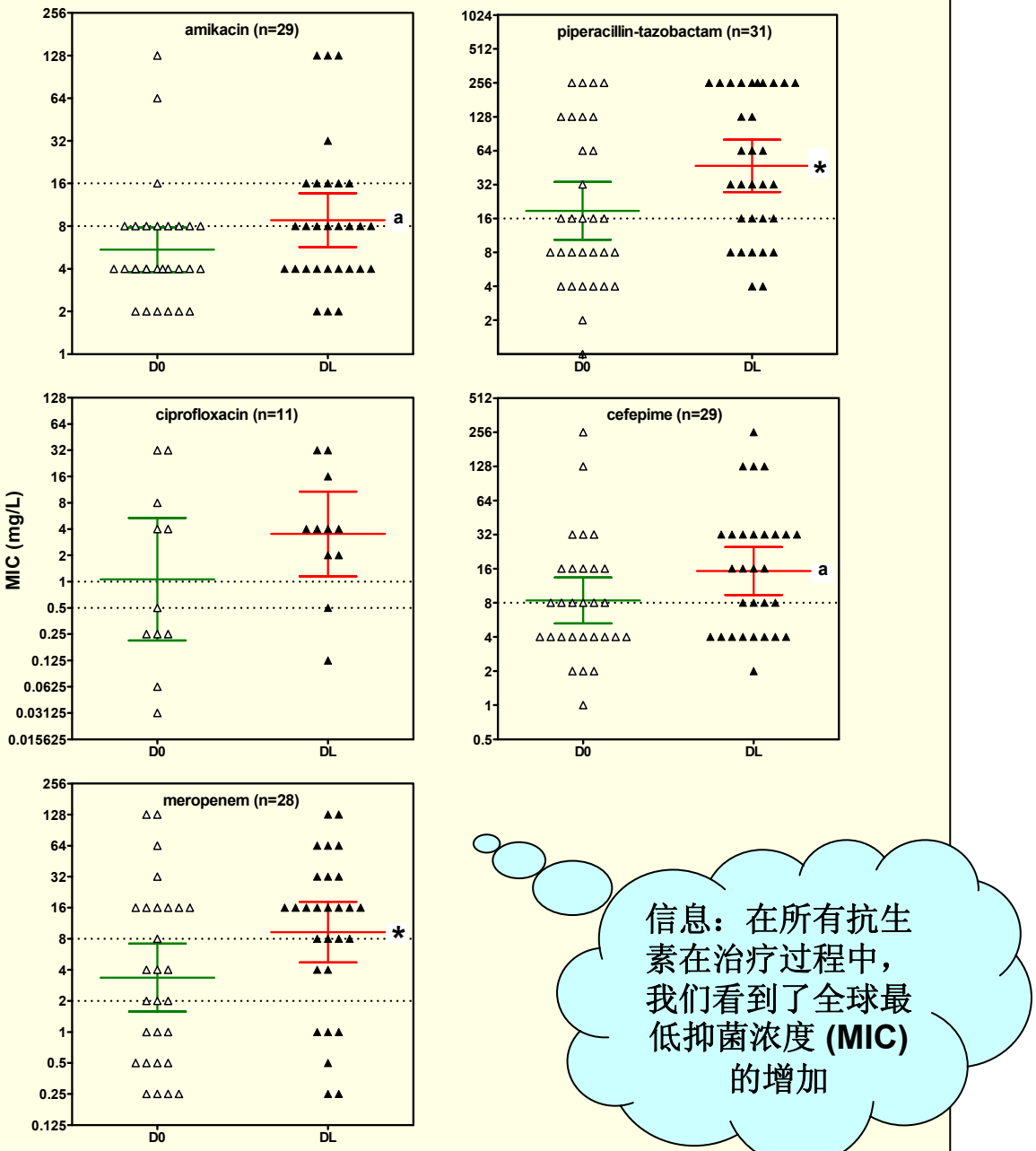
治疗时仍然有效吗？

- D0：初始分离菌
  DL：获得最后分离菌
- 几何平均数的个别值（95% CI）
- S（最低线）和R（最高线）EUCAST折点

* 配对t检验（双尾）和Wilcoxon非参数检验p <0.05

[a]只使用Wilcoxon非参数检验p <0.05

注：由D0和DL之间以时间进行的分层没有提供任何线索（数字过低）



信息：在所有抗生素在治疗过程中，我们看到了全球最低抑菌浓度 (MIC) 的增加

治疗中隐藏的风险（在医院...）

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

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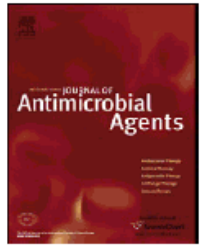
journal homepage: http://www.elsevier.com/locate/ijantimicag



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*

其实，耐药很容易
即使是在一个封闭的系统.....

*产气肠杆菌接触*抗革兰氏阴性菌β-内酰胺类14天，最低抑菌浓度0.25，根据最低抑菌浓度测定每天重新调整浓度

株	初始			透射电子显微镜下			回复体		
	最低抑菌浓度（毫克/升）[a]			最低抑菌浓度（毫克/升）			最低抑菌浓度（毫克/升）		
	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] 粗体显示的数字表示该值>肠杆菌的R断点（EUCAST的MEM [8]和FEP [4]；BSAC和比利时的TEM [16]）
[b] 斑点印迹与antiOmp36抗体一起应用；减去一个孔蛋白阴性菌株后信号进行量化以取得灰度值（ImageJ软件）；负值表示信号低于背景信号
[c] ESBL TEM 24 (+)；[d] ESBL (-) 和AmpC (+) [高水平][e] 根据EUCAST为中水平(I)

Nguyen等（LDRI博士后）
于2011年4月8日韩国首尔举行的第8届ISAAR提交，额外工作正在进行中

一个简单的实验……

*产气肠杆菌*接触抗革兰氏阴性菌β-内酰胺类14天，最低抑菌浓度0.25，根据最低抑菌浓度测定每天重新调整浓度

株	初始			透射电子显微镜下			回复体		
	最低抑菌浓度（毫克/升）[a]			最低抑菌浓度（毫克/升）			最低抑菌浓度（毫克/升）		
	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

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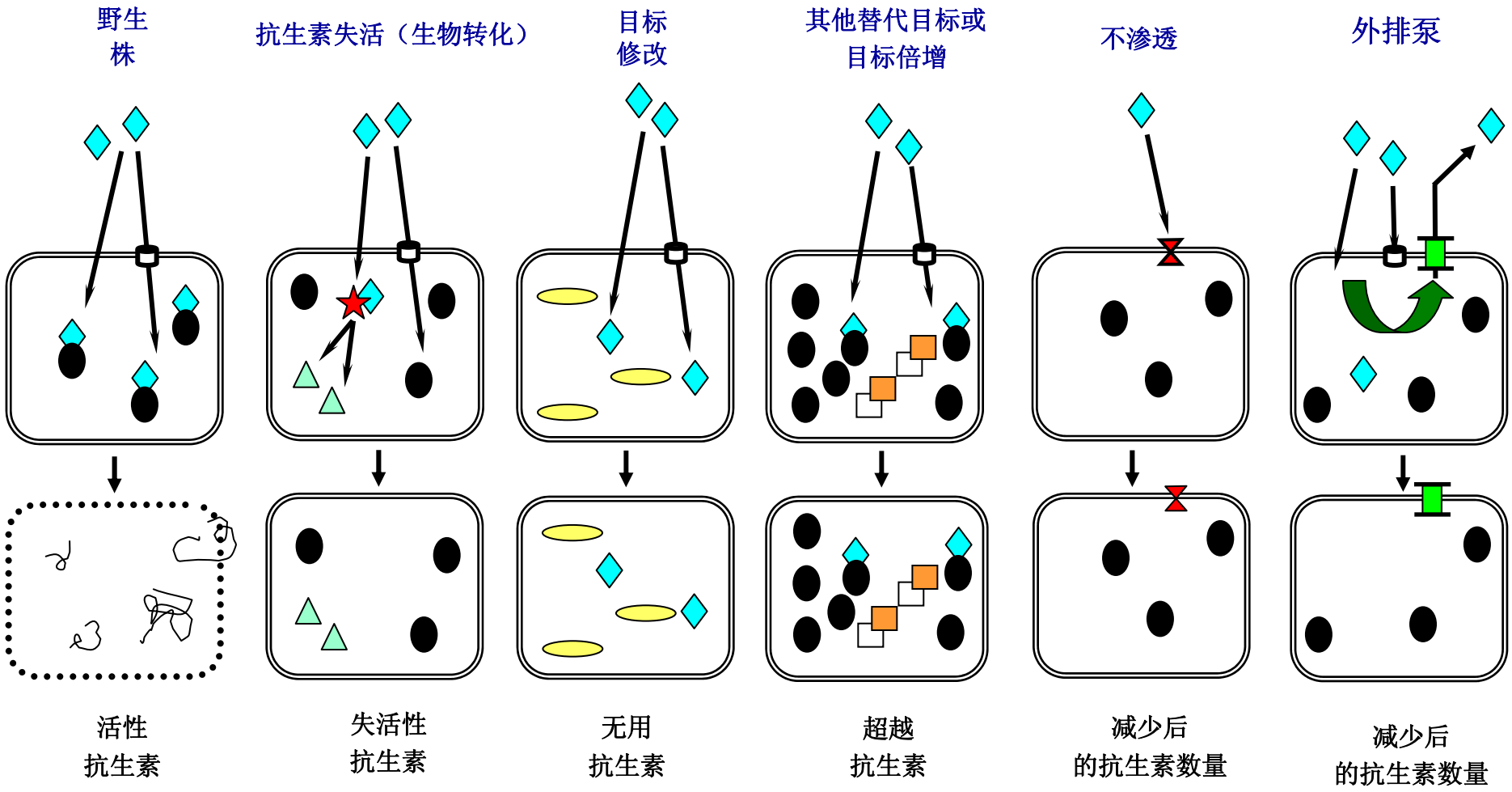
[c] ESBL TEM 24 (+)；[d] ESBL (-) 和AmpC (+) [高水平][e] 根据EUCAST为中水平(I)

N[illegible]en[illegible]DRI博[illegible]士后）
于20[illegible]月8日[illegible]英国[illegible]举行的第8届[illegible]R[illegible]报道；[illegible]作正在进行中

亚抑菌亚浓度选择了耐药性！

抗生素耐药性：主要机制的简短概述



主要细菌耐药机制在呼吸道感染的重要性，以及如何加以对抗

生物	机制	怎么办？	成功了吗？
肺炎链球菌	目标突变 与青霉素结合的PBP2X	增加β-内酰胺类抗生素的剂量	局部 （最低抑菌浓度□4毫克/升）
	大环内酯类、林可酰胺类和链霉杀阳菌素类的目标突变	无（高耐药性）	否
	大环内酯类外排	增加剂量（但困难）	具争议性
	氟喹诺酮类外排	避免氟喹诺酮类外排（环丙沙星、吉米沙星）	是（如果使用莫西沙星）

主要细菌耐药机制在呼吸道感染的重要性，以及如何加以对抗

生物	机制	怎么办？	成功了吗？
流感嗜血杆菌	β-内酰胺酶	添加β-内酰胺酶抑制剂	是（但有毒性）
	β-内酰胺类目标突变	高耐药性	否
卡他莫拉菌	β-内酰胺酶	添加β-内酰胺酶抑制剂	是（但有毒性）
金黄色葡萄球菌	抗甲氧西林	使用万古霉素、利奈唑胺或达托霉素	是，但有限制（万古霉素）和毒性
肺炎支原体	大环内酯类目标突变	无（高耐药性）	否

主要细菌耐药机制在呼吸道感染的重要性，以及如何加以对抗

生物	机制	怎么办？	成功了吗？
肠杆菌	β-内酰胺酶（包括ESBL和碳青霉烯酶）	改变抗生素	是（但在多重耐药性的情况下有困难）
	氟喹诺酮类目标突变	使用最强力的氟喹诺酮类（解离耐药性）	中度
	外排（影响几类）	“微调”抗生素的选择（根据抗菌谱）	中度

主要细菌耐药机制在呼吸道感染的重要性，以及如何加以对抗

生物	机制	怎么办？	成功了吗？
铜绿假单胞菌	β-内酰胺酶（包括ESBL）	改变抗生素	是（但在多重耐药性的情况下有困难）
	渗透率下降	选择具有较高渗透性的抗生素	中度
	氟喹诺酮类目标突变	使用最强力的氟喹诺酮类（解离耐药性）	中度
	外排（影响几类）	“微调”抗生素的选择（根据抗菌谱）	中度

流行病学

流行病学：原则

流行病学（监控）研究必须

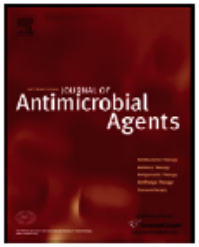
- 根据**地域**恰当调整，以应对病原体的类型
  - *肺炎链球菌*□区域或国家层面
  - *铜绿假单胞菌*□根据医院甚至病房
- **全面**
  - 正确的患者群覆盖、并发的疾病以及相关的机体
  - 在一个给定的时期内分离出足够多数量的菌株
- 使用**适当的阐释标准**（折点）

肺炎链球菌：比利时范例

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

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]

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[b] *Laboratorium microbiologie, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium*
[c] *Laboratoire de microbiologie, Cliniques Notre-Dame de Grâce, Gosselies, Belgium*
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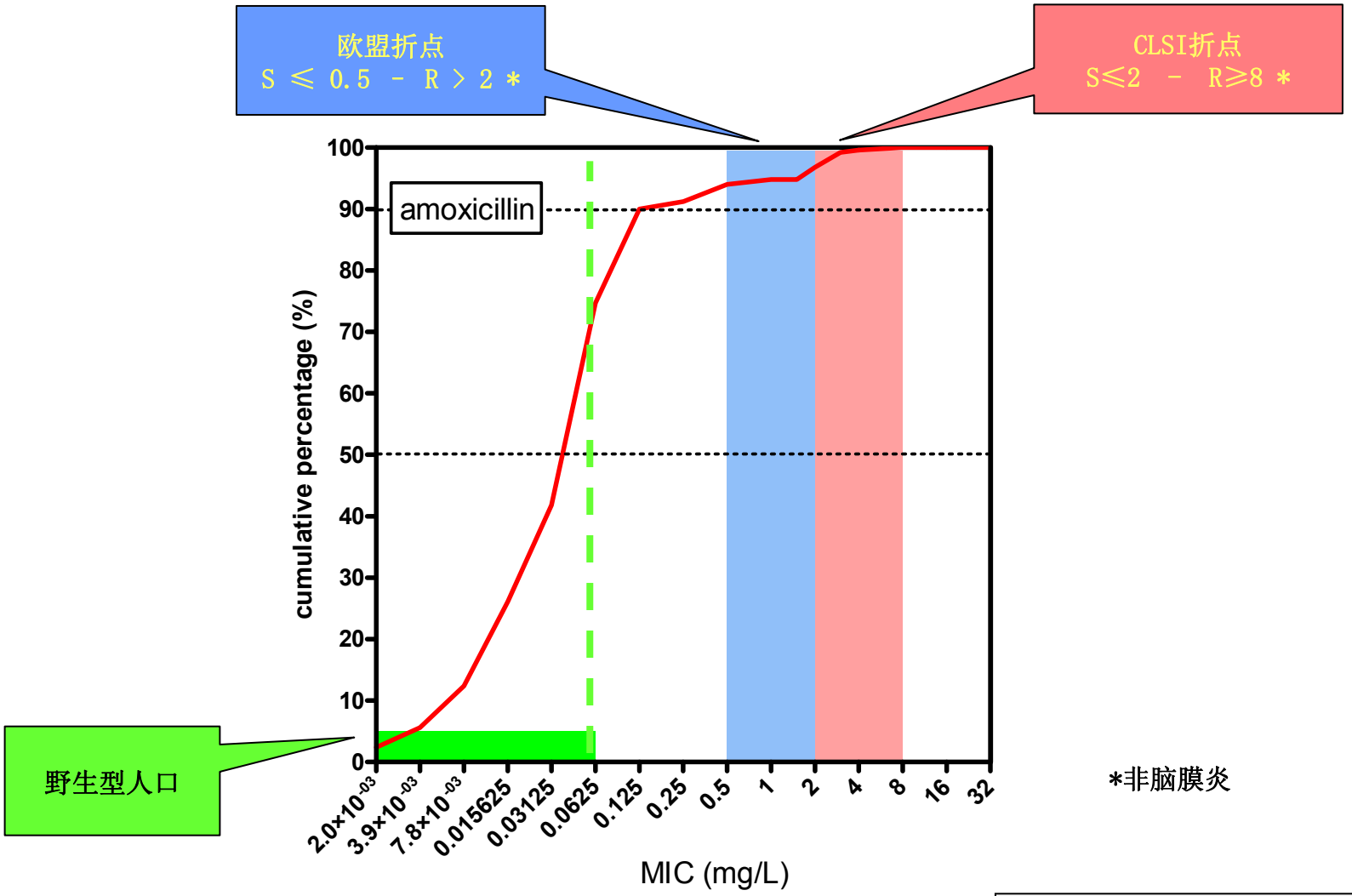
[e] *Afdeling pneumologie, O.L.V. Ziekenhuis, Aalst, Belgium*
[f] *Clinique des maladies infectieuses, Hôpital Erasme, Brussels, Belgium*
[g] *Laboratoire de microbiologie, CHU Saint-Pierre, Brussels, Belgium*
[h] *Service des urgences, Cliniques universitaires Saint-Luc, Brussels, Belgium*
[i] *Laboratoire de microbiologie, Cliniques universitaires Saint-Luc, Brussels, Belgium*
[j] *Laboratoire de microbiologie, CHU Mont-Godinne, Yvoir, Belgium*

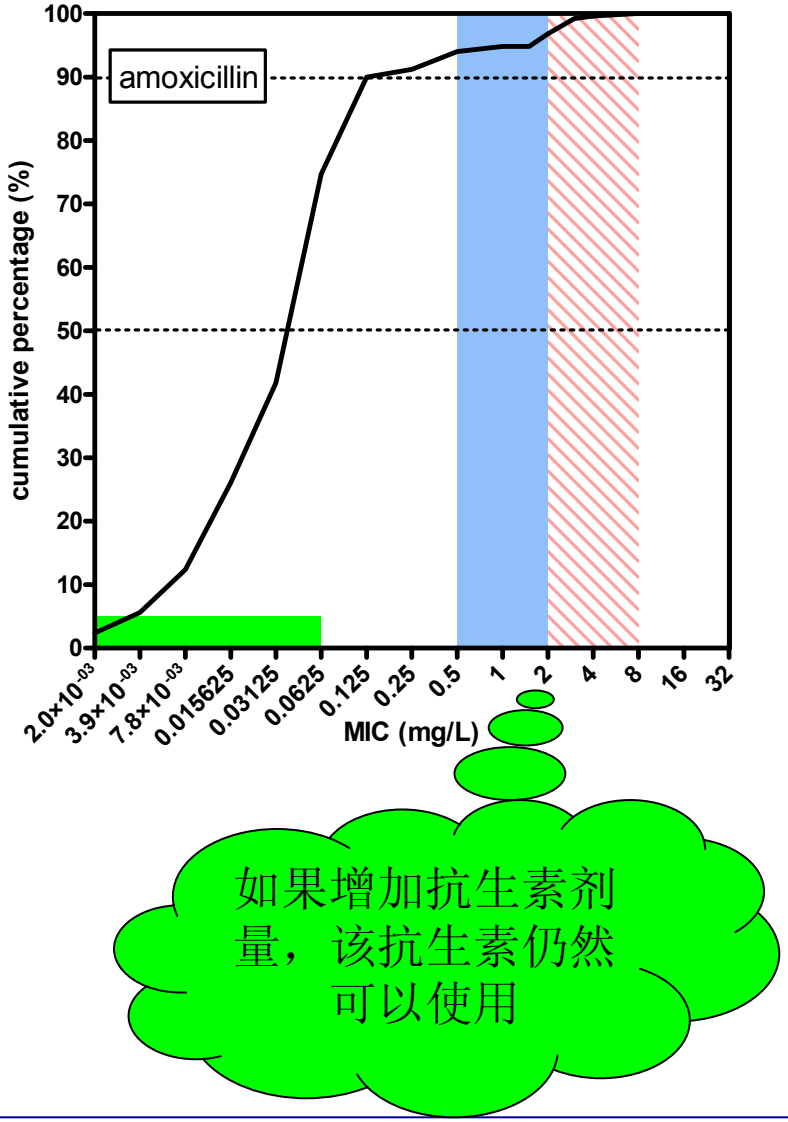
肺炎链球菌：比利时的一个范例

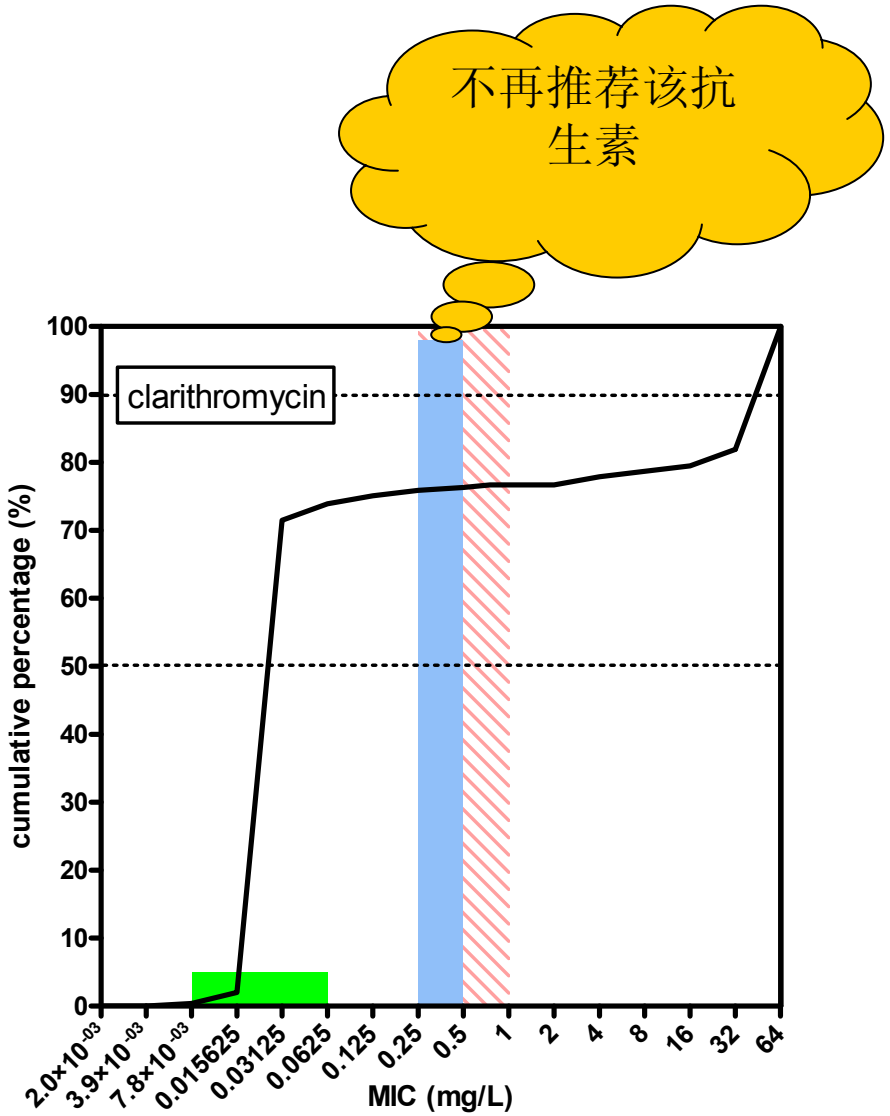


*非脑膜炎

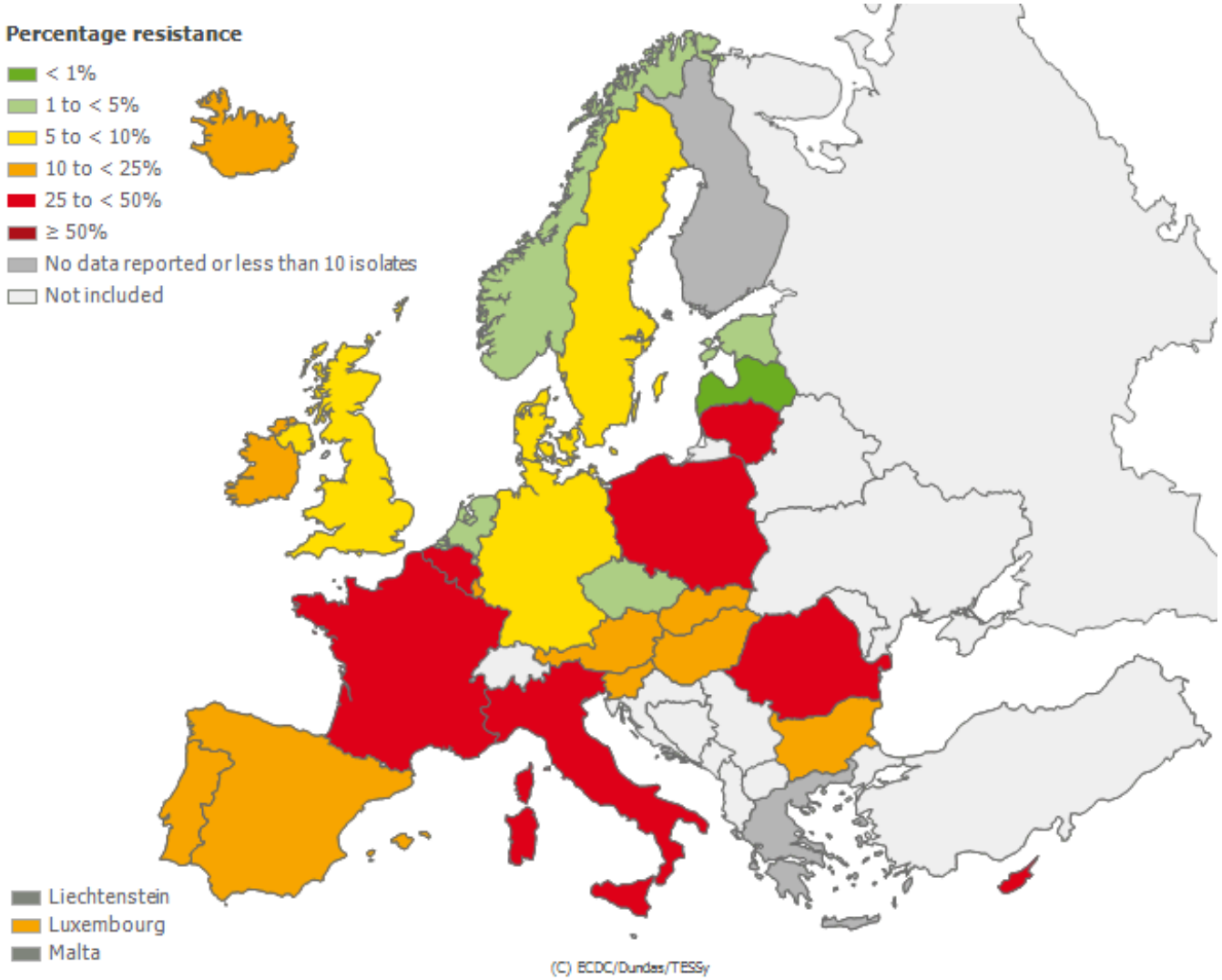
比利时数据：
Lismond等Int.J. Antimicrob Agents.2012年3月;39(3):208-16.

肺炎链球菌：如何制定抗生素政策





*肺炎链球菌*大环内酯类耐药性的欧洲调查

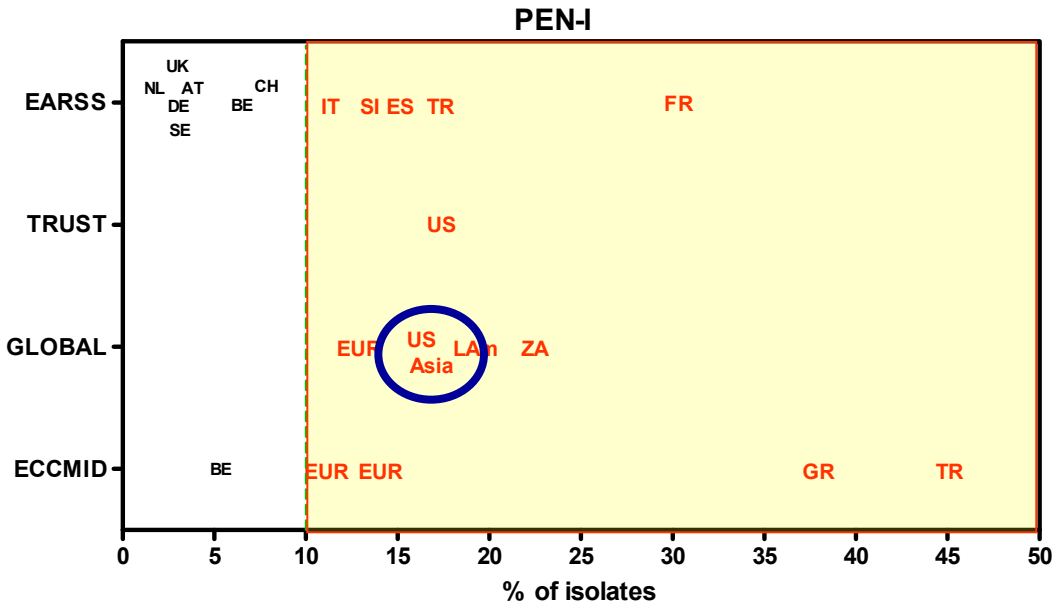


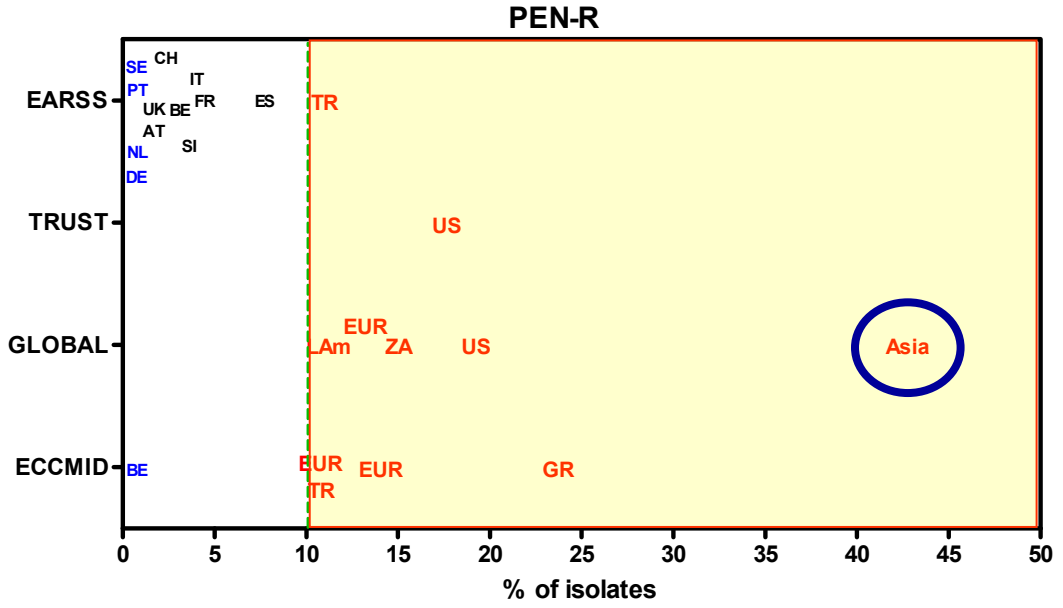
http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/maps_report.aspx

肺炎链球菌
耐药性
*国际范例**

*耐药监测系统或发表文章中对青霉素耐药性的分析（社区获得性肺炎为主要适应症）
（肺炎链球菌）

- EARSS：欧洲抗生素耐药性监测系统
- TRUST：美国耐药现状研究
- GLOBAL：左氧氟沙星杀菌活性全球现状
- ECCMID：第18至20届欧洲临床微生物学和传染病大会摘要





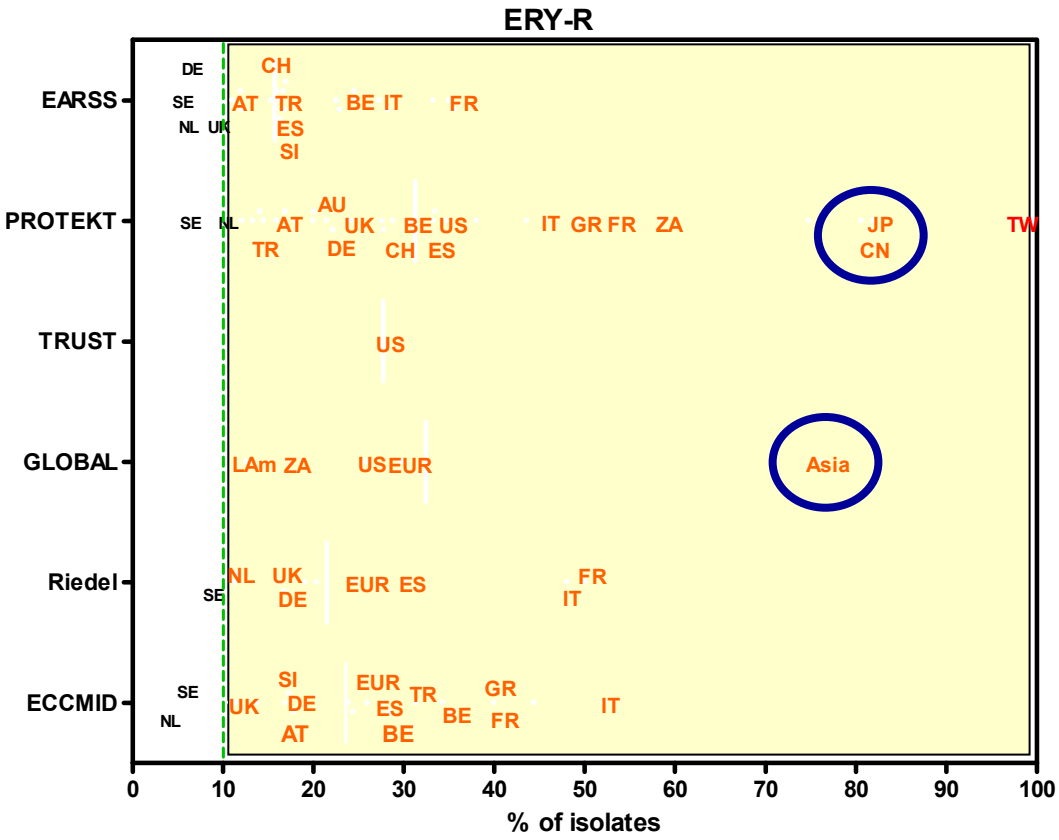
Carbonnelle等，拟定中

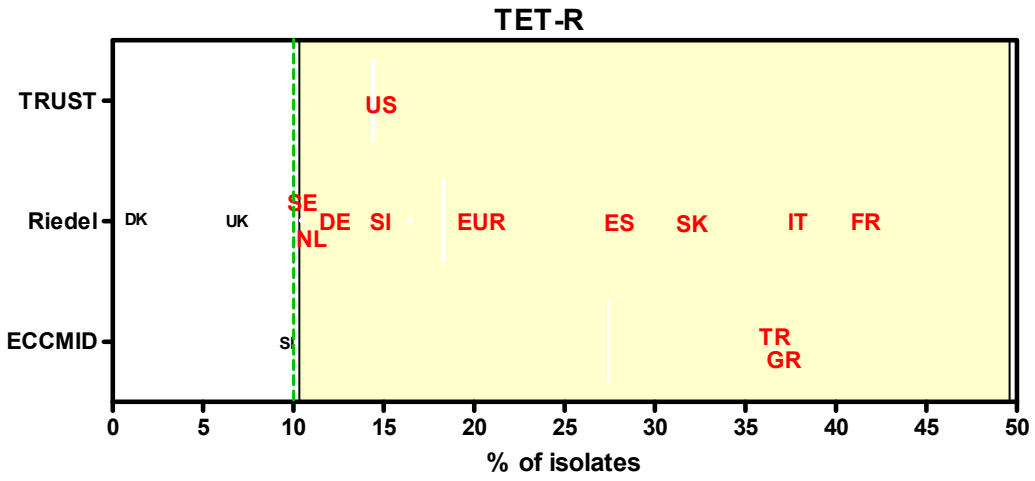
肺炎链球菌
耐药性
*国际范例**

*耐药监测系统或发表文章中对红霉素和多西环素耐药性的分析（社区获得性肺炎为主要适应症）
（肺炎链球菌）

- EARSS：欧洲抗生素耐药性监测系统
- PROTEKT：酮内酯类泰利的前瞻性耐药菌追踪和流行病学
- TRUST：美国耐药现状研究
- GLOBAL：左氧氟沙星杀菌活性全球现状
- Riedel：Eur J Clin Microbiol Infect Dis.2007年7月;26（7）:485-90.
- ECCMID：第18至20届欧洲临床微生物学和传染病大会摘要

Carbonnelle等，拟定中





信息：设计和使用调查

- 各国应该知道本国的耐药模式！

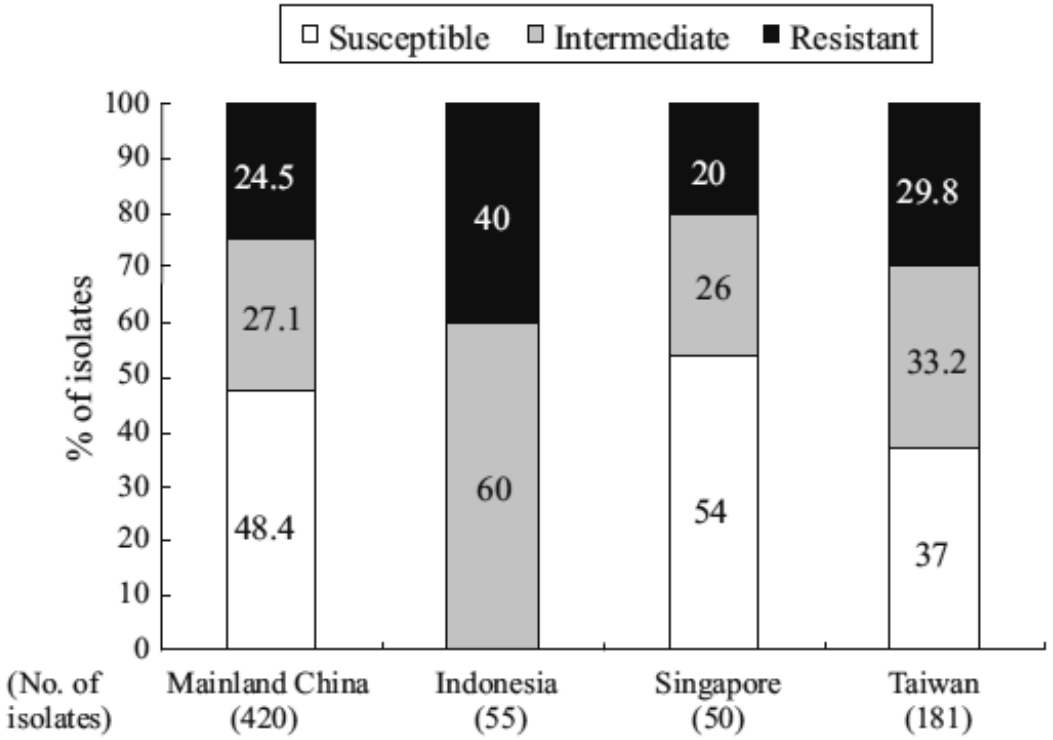


Fig. 1. Distribution of susceptibility of *Streptococcus pneumoniae* isolated from patients in Mainland China, Taiwan, Singapore and Indonesia based on the break-points of oral penicillin V [11].

H. Wang等Intern. J. Antimicrob. Agents *38 (2011) 376 - 383*

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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

Asia Pacific Foundation for Infectious Diseases (APFID), Seoul, South Korea[a]; Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea[b]; Siriraj Hospital, Mahidol University, Bangkok, Thailand[c]; Beijing Children's Hospital Affiliated to Capital Medical University, Beijing, China[d]; Peking Union Medical College Hospital, Beijing, China[e]; Shanghai Children's Hospital, JiaoTong University, Shanghai, China[f]; Princess Margaret Hospital, Kwai Chung, Hong Kong[g]; National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan[h]; Institute for Medical Research, Kuala Lumpur, Malaysia[i]; Antimicrobial Resistance Surveillance Reference Laboratory, Research Institute for Tropical Medicine, Manila, Philippines[j]; Faculty of Medicine, University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam[k]; Madras Medical Mission, Chennai, India[l]; Kyushu University Hospital, Fukuoka, Japan[m]; University of Colombo, Colombo, Sri Lanka[n]; King-Saud University Hospital, Riyadh, Saudi Arabia[o]; and Department of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Suwon, South Korea[p]

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等Antimicrob.Agents Chemother.2012, 56(3):1418.

一项亚洲人调查：病人

TABLE 1 Demographic and clinical characteristics of patients with pneumococcal infection

Characteristic	No. of patients/total no. (%) (n = 2,100)
Type of infection	
Pneumonia	1,680 (80.0)
Acute sinusitis	108 (5.1)
Meningitis	102 (4.9)
Primary bacteremia	67 (3.2)
Acute otitis media	54 (2.6)
Empyema	17 (0.8)
Abscess	17 (0.8)
Peritonitis	10 (0.5)
Other	45 (2.1)
Concomitant bacteremia	284 (13.5)
Underlying disease	
Pulmonary disease	337/1,656 (20.4)
Cerebrovascular disease	134/1,631 (8.2)
Solid tumor	146/1,643 (8.9)
Hematologic malignancy	30/1,630 (1.8)
Chronic renal disease	79/1,637 (4.8)
Chronic liver disease	70/1,653 (4.2)
Cardiovascular disease	108/1,633 (6.6)
Diabetes mellitus	225/1,649 (13.6)
Comorbid condition	
Smoking	389/1,540 (25.3)
Corticosteroid use	49/1,603 (3.1)
Immunosuppressant use	12/1,599 (0.8)
Neutropenia	23/1,599 (1.4)

Kim等Antimicrob.Agents Chemother.2012, 56(3):1418.

一项亚洲人调查：我们与青霉素处于什么关系？

留意最低抑菌浓度！

TABLE 2 Susceptibilities to antimicrobial agents of *Streptococcus pneumoniae* isolates from patients with pneumococcal infections in 11 Asian countries[c]

Country	No. of cities (no. of hospitals)	No. of isolates (invasive[a]/ meningeal isolates)	Resistance to: Penicillin Nonmeningeal isolates MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	% I	% R
China	8 (14)	642 (33/5)	1	4	11.0	2.2
Hong Kong	1 (2)	196 (8/0)	0.25	2	1.5	0
India	2 (3)	23 (NA/NA)	<0.03	1	0	0
Japan	1 (1)	18 (0/0)	0.5	1	0	0
South Korea	3 (13)	327 (70/12)	1	2	1.9	0.3
Malaysia	7 (9)	165 (118/13)	<0.03	0.5	0	0
Philippines	5 (5)	118 (49/3)	<0.03	0.06	0	0
Sri Lanka	1 (1)	19 (9/0)	1	2	0	0
Taiwan	3 (3)	231 (30/0)	1	2	0.4	0
Thailand	1 (2)	212 (24/1)	0.25	2	0.5	0
Vietnam	3 (7)	233 (24/6)	1	2	0.9	0
Total	40 (60)	2,184 (365/40)	0.5	2	3.9	0.7

[a] Invasive strains were isolated from sterile sites such as blood, CSF, pleural fluid, ascites, and joint fluid in patients with pneumococcal infections.

[b] NA, not available.

[c] The MIC breakpoints for pneumococcal isolates were determined according to the CLSI guidelines

Kim等Antimicrob. Agents Chemother. 2012, 56(3):1418.

折点的问题

CLSI（美国）与EUCAST（美国）折点比较

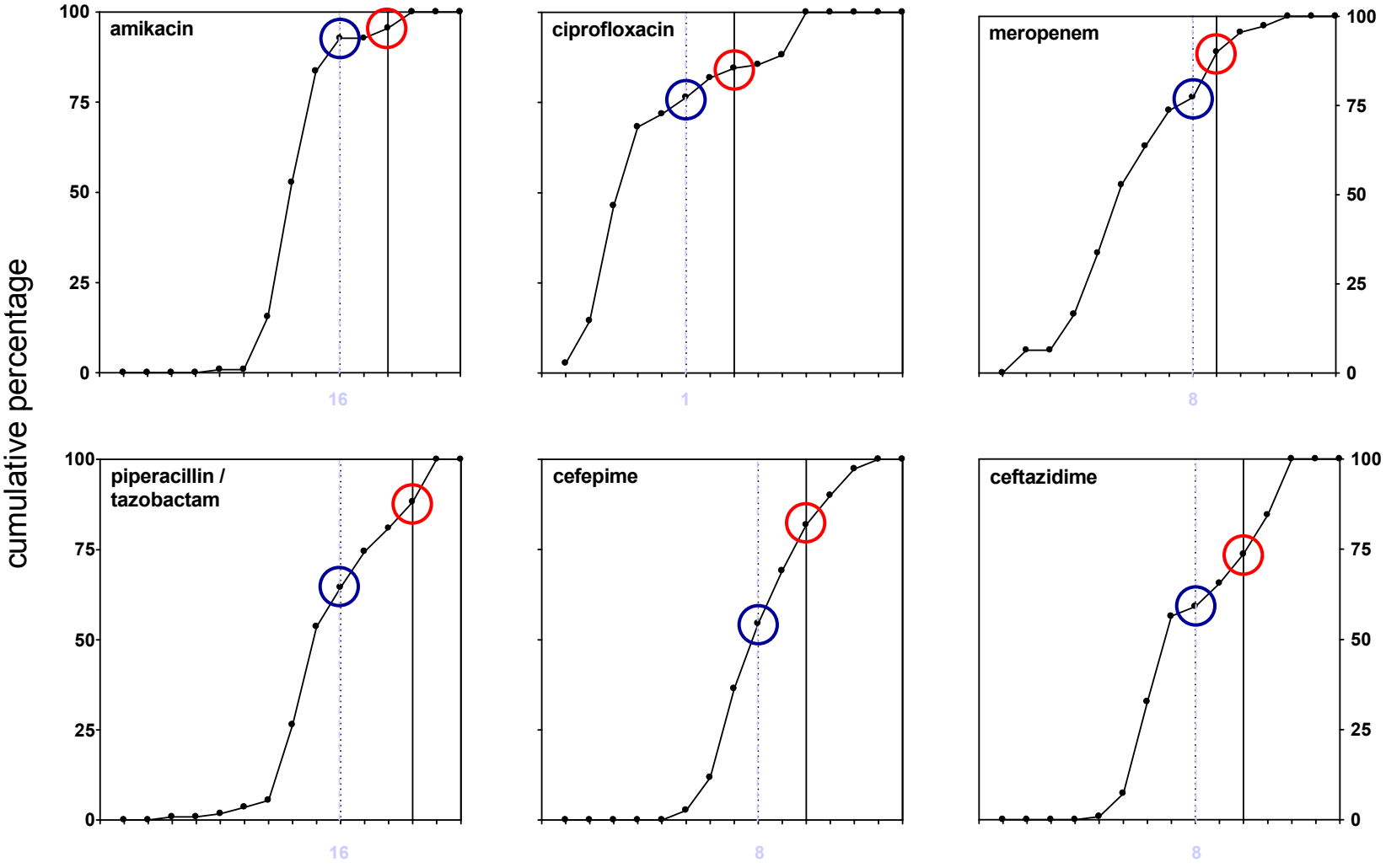
CLSI折点

- 早已众所周知过高（过于乐观）
- 不再是官方机构（因此名称从NCCLS（国家临床实验室标准委员会）变更为CLSI（临床实验室标准研究所））
- 设有一个非完全透明的设定体系（受到行业的高度影响）

EUCAST折点

- 完全独立于行业之外（由欧盟资助）
- 非常依赖PK/PD和临床数据
- 往往要比CLSI折点低得多（更严谨）

*铜绿假单胞菌*不同折点示例



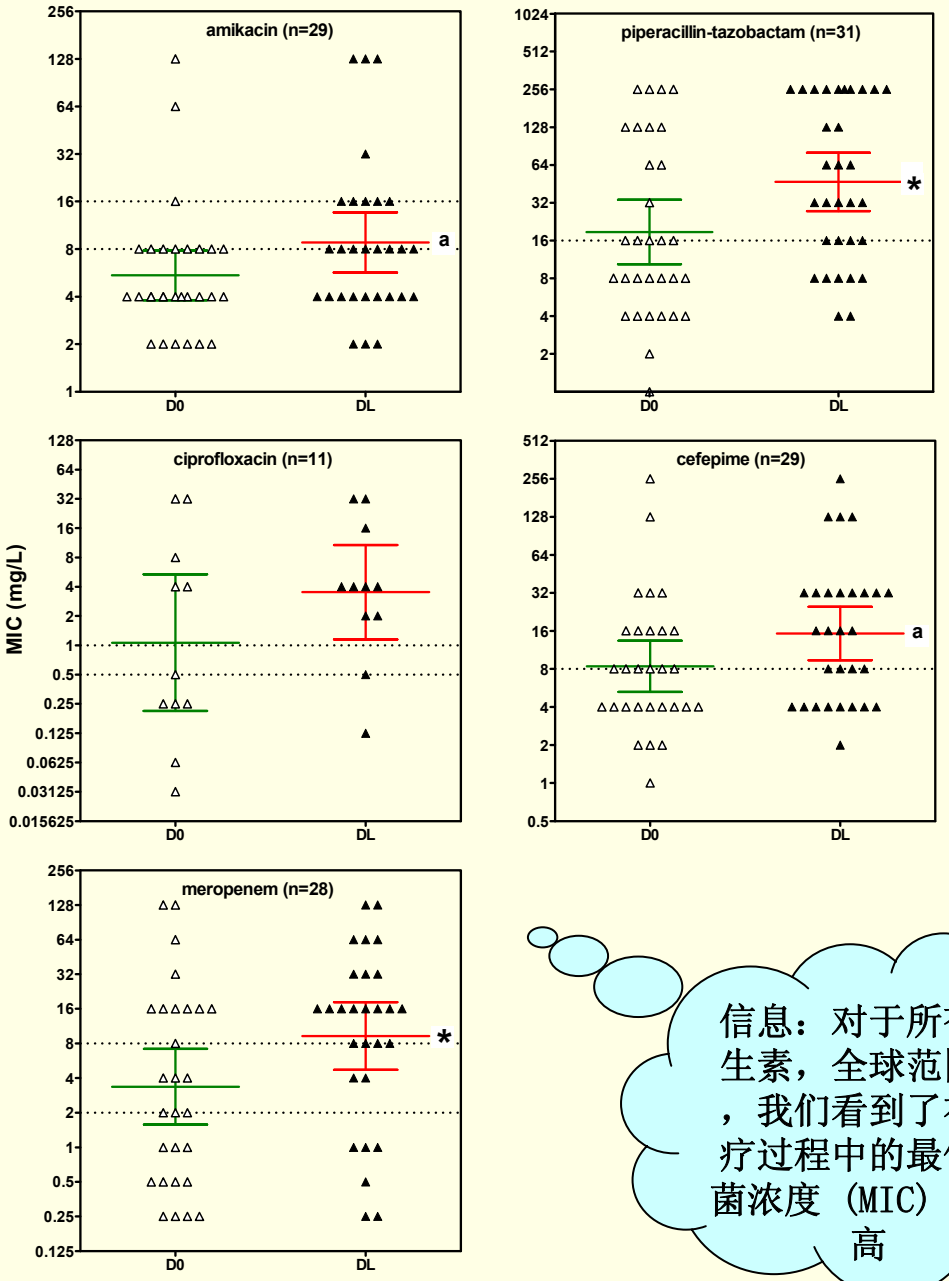
治疗时仍然有效吗？

- D0：初始分离菌
  DL：获得最后分离菌
- 几何平均数的个别值（95% CI）
- S（最低线）和R（最高线）
  EUCAST折点

* 配对t检验（双尾）和Wilcoxon非参数检验p <0.05

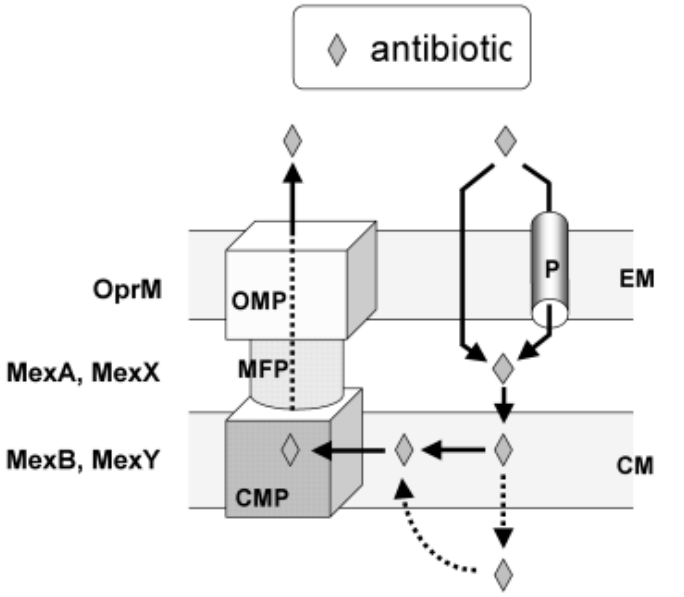
[a]只使用Wilcoxon非参数检验p <0.05

注：由D0和DL之间以时间进行的分层没有提供任何线索（数字过低）

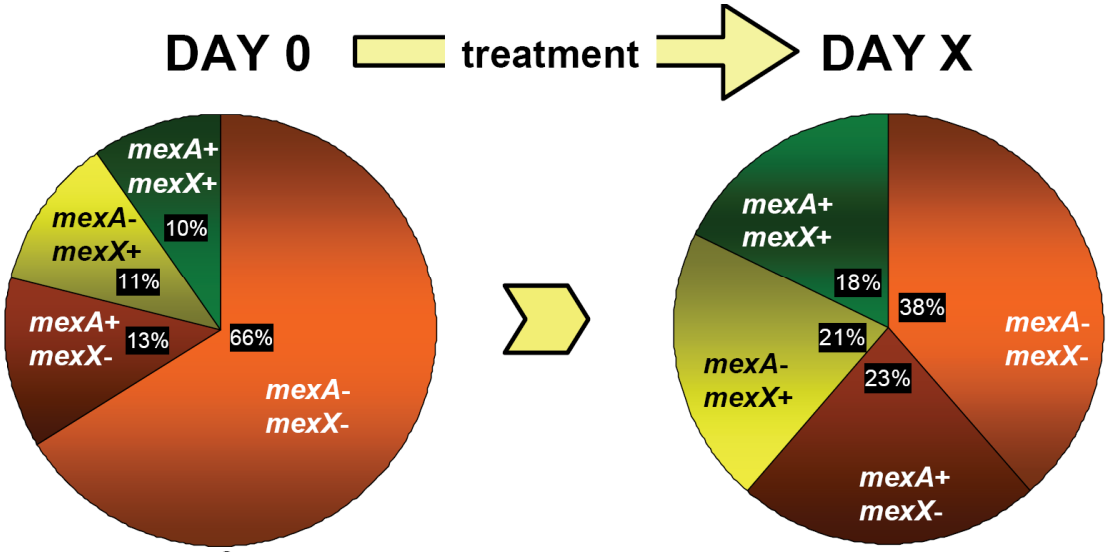


信息：对于所有抗生素，全球范围内，我们看到了在治疗过程中的最低抑菌浓度（MIC）的增高

治疗过程中
*铜绿假单胞菌*的外排介导耐药性



CMP: cytoplasmic membrane protein
MFP: membrane fusion protein
OMP: outer membrane protein
CM: cytoplasmic membrane
EM: external membrane
P: porin



结论

- 对抗生素的耐药性是一个普遍的问题，也是抗生素使用的固有问题
- 唯一真正的解决办法是不使用抗生素或大大减少抗生素使用
  （有力证据表明，越多使用抗生素，耐药菌株的百分比会越高）
- 因此我们急需找出控制细菌的替代方法
  - 通过（接种疫苗等）从源头阻止其繁殖
  - 或使其变成无害的（抗毒力策略）

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

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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).

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*

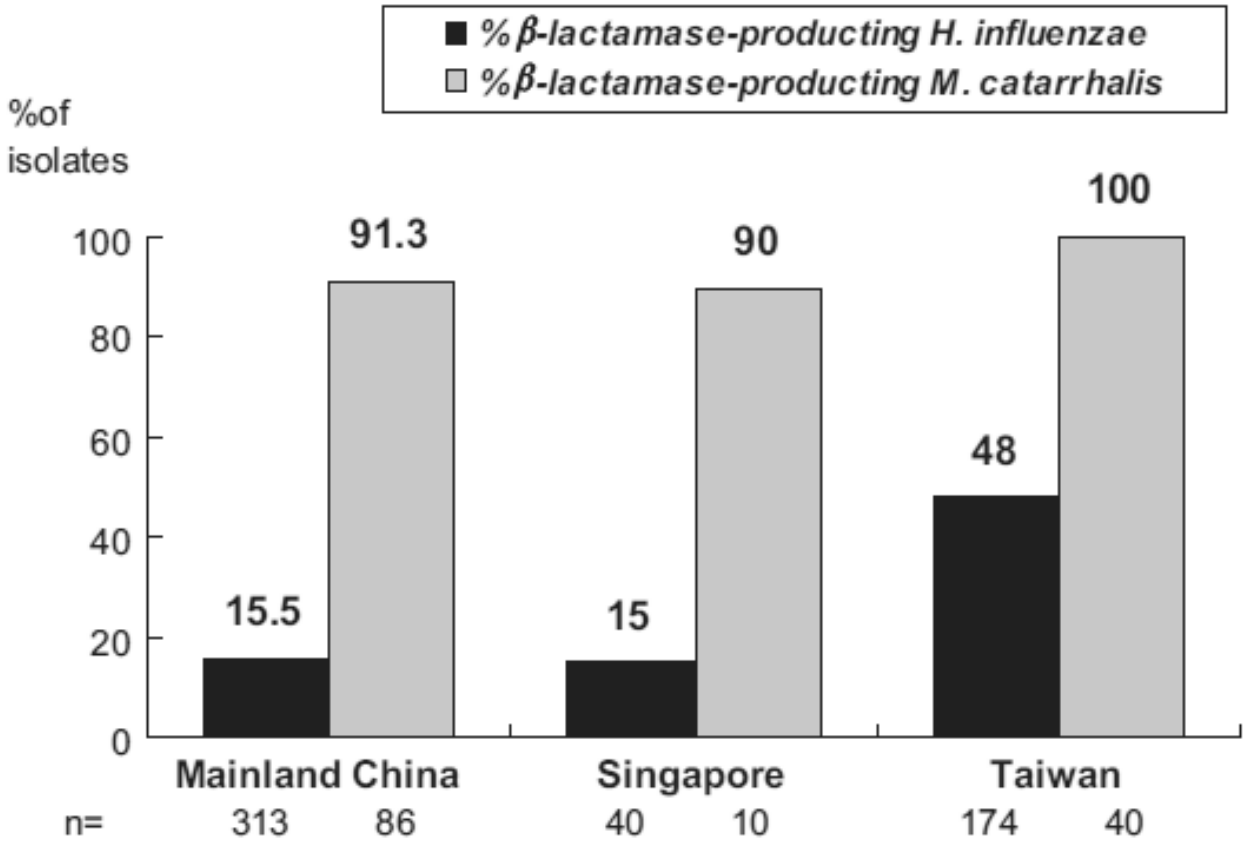

Fig. 2. Proportions of β-lactamase production amongst *Haemophilus influenzae* and *Moraxella catarrhalis* isolates from Asian countries.

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).

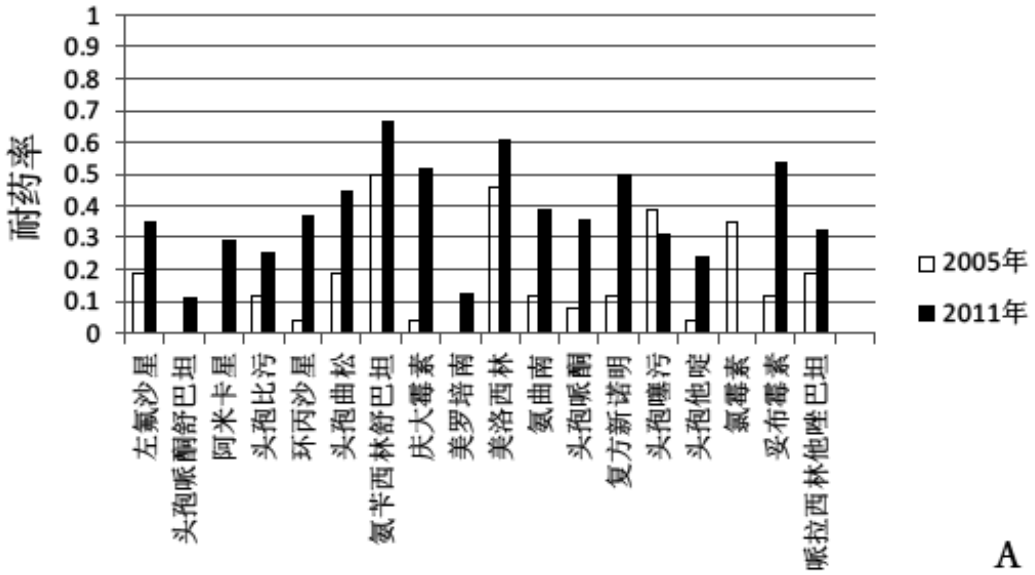

图2　两种主要革兰阴性杆菌2005年与2011年的耐药率比较。A：铜绿假单胞菌；B：鲍曼不动杆菌。

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