中國醫藥大學
China Medical University

CRE in ICU

Challenges and Opportunities

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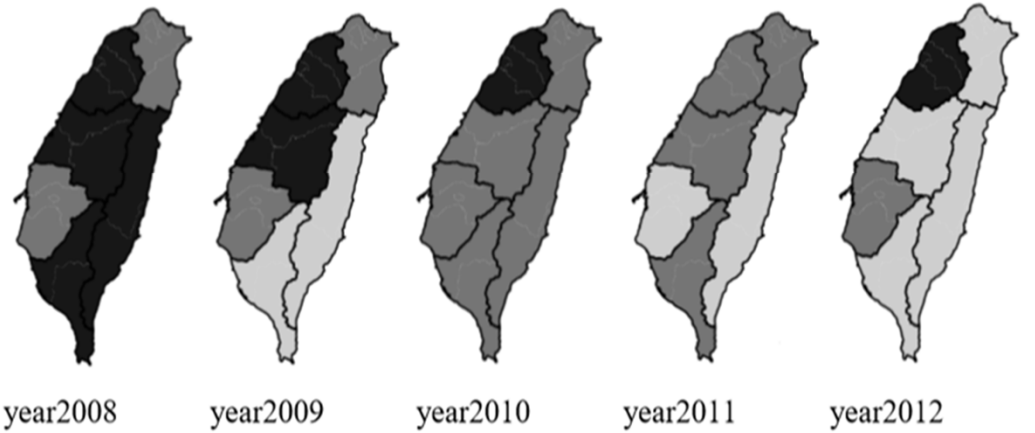
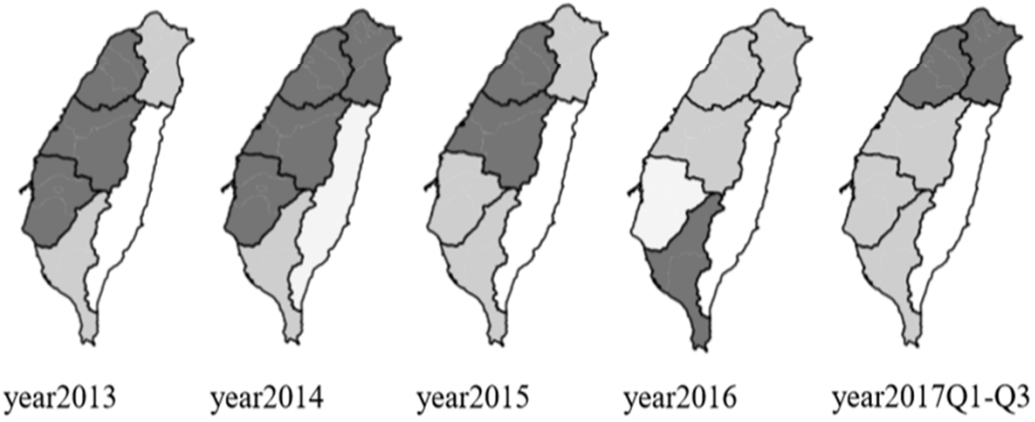
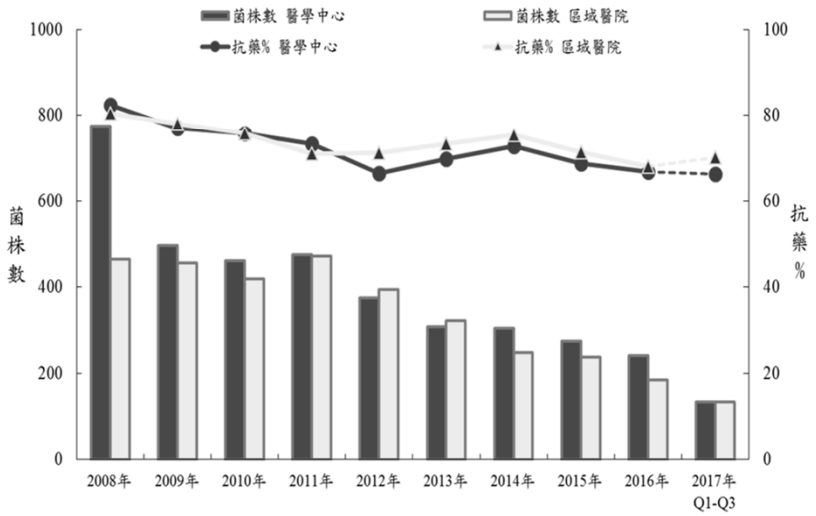
2008 至2017 年醫學中心及區域醫院加護病房
醫療照護相關感染MRSA百分比分佈圖

2008 至 2017 年第 3 季，區域級以上醫院加護病房醫療照護相關感染 MRSA 比率在 6 區的分布如圖 20。於 2008 年以高屏區(84.8%)較高；2017 年第 3 季 MRSA 比率以台北區(72.4%)為最，北區(70.8%)次之。

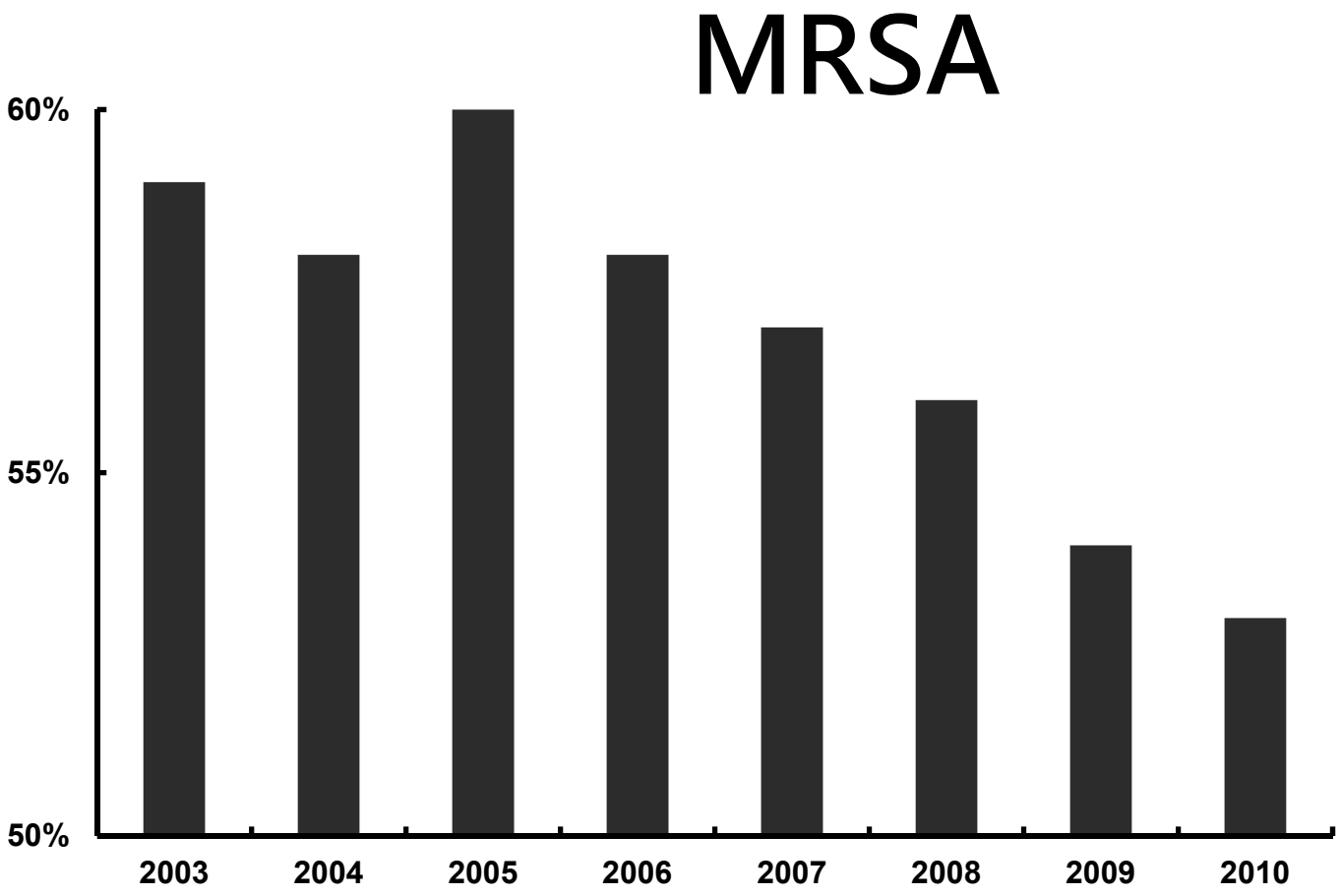




加護病房醫療照護相關感染抗藥菌菌株分佈



CSMH Surveillance of Resistant Pathogens (1)



Pandrug-Resistant *Acinetobacter baumannii*

台灣土產 全抗藥性 AB菌肆虐 死亡率達六成 醫學中心衝擊大

簡稱PDRAB 台灣獨有超強細菌 無藥可醫 台大醫院院內感染 它問題最大 勤洗手、穿隔離衣、管制抗生素暫可阻絕

本報醫藥組／調查報導

「你的家人感染AB菌，小心抗藥性很強！」AB菌是什麼？很多民眾從沒聽過，甚至直覺以為是優酪乳廣告所稱的細菌。這種醫院中的細菌非常可怕，已嚴重威脅重症病患。

抗生素濫用導致細菌抗藥性升高在台灣特別嚴重，Acinetobacter baumannii（AB菌）正式名稱為「鮑氏不動桿菌」，正迅速在醫院肆虐，甚至嚴重到出現「全抗藥性AB菌」）Pandrug-Resistant AB，簡稱PDRAB），沒有抗生素可以殺死這種超強的細菌。

台大醫院感染科主治醫師薛博仁兩年前在美國疾病管制中心「新興傳染疾病」（Emerging Infectious Diseases）期刊發表論文，指出PDRAB在台大醫院迅速出現，從一九九八年之前沒有紀錄，到兩千年台大已從七十七名病患身上分離出一百九十九株PDRAB。

薛博仁表示，台大醫院院內感染病原菌中，以抗藥性極強的AB菌問題最大，這種菌散布在病房內，加護病房尤其嚴重，這種菌株的感染會造成病患嚴重的菌血症與肺炎。

現況到底有多嚴重？醫院雖不願承認，但最近幾次感染科醫學會上，PDRAB是大家最棘手的問題。一位不願具名的感染科醫師大膽估計，從北到南，醫學中心幾乎全都已「淪陷」，最近甚至有區域醫院護士表示，她們醫院裡也檢出這隻全抗藥性的細菌。

「這是台灣土產喔！」一位感染科醫師如此形容PDRAB，這個名詞正是薛博仁提出，薛的論文發表後，美國疾病管制中心才正視PDRAB的問題，並預期會愈來愈嚴重。

振興醫院感染科主任周明淵表示，多重抗藥性的AB菌在台灣，感染率約是一千名住院病人有七、八人感染。全抗藥性AB菌（PDRAB）感染率較難估計。

至於感染PDRAB的病患死亡率，台大內科醫師郭律成等人去年發表的研究顯示，從一九九九年一月到二〇〇二年四月，治療卅名感染此種細菌的菌血症病患，十八名死亡，死亡率高達六成。

郭律成說，PDRAB可說是台灣獨有的超強細菌，沒有任何藥物可以醫治，國外文獻報告陳述的AB菌雖然也是多重抗藥性，但至少還有兩、三種抗生素有效。

一位醫學中心的醫師指出，抗生素管制不確實是PDRAB肆虐的原因之一，醫師普遍使用最後一線抗生素，導致細菌不斷突變，終於形成對所有抗生素都有抗性的PDRAB。以泰寧（Tienam）這最後一線抗生素為例，剛出來的頭兩、三年，各科醫師必須照會感染科醫師才能用，現在則因為用得普遍，幾乎都不再會感染科。

台大醫院感染科主任張上淳表示，此菌是接觸傳染，雖不像SARS病毒飛沫傳染那麼可怕，但會藉由人手或器材傳播，尤其醫護人員，如果忘了洗手就去照顧一位病人，就容易傳染。

台大小兒感染科醫師李秉穎直言，AB菌很容易突變，第一線抗生素幾乎都沒效果，必須以後線抗生素來治療，但細菌很聰明，當醫師使用後線抗生素來治療時，細菌又再度突變，導致PDRAB出現，病患只有靠自身的免疫力來殺死細菌。

如何根本解決AB菌造成的感染問題？郭律成建議，應該採取嚴格的院內感染管制措施與抗生素管制，尤其是使用最後線抗生素時，院方應該嚴格要求一定要照會感染科醫師。

李秉穎則表示，掛牌子標示感染此菌的病患，醫護人員接觸病患前後必須徹底洗手，並換穿隔離衣阻絕醫護人員把細菌帶到其他病患身上。（記者許峻彬、魏忻忻、吳靜美、施靜茹、宋豪麟、陳惠惠調查採訪）

細菌不認識它 老抗生素上陣 對付全抗藥性AB菌

感染專家提建議 •找回被遺忘的抗生素 也許細菌已無抗藥性 •從感染源頭開始控制 讓超級細菌自我淘汰

【記者宋豪麟／台北報導】後抗生素時代來臨，我們有什麼「武器」對抗超強細菌？台灣出現全抗藥性AB菌，醫界認為，面對全抗藥性細菌出現，除了加強醫師使用抗生素訓練、研發新的抗生素外，就是嘗試古老、已漸不使用的抗生素。

國防醫學院藥學系教授胡幼圃解釋，本來我們有許多抗生素對不同細菌分別構築防線，像盤尼西林、健他黴素可對抗第一線的嗜氧菌，metronidazole用在第一線的厭氧菌。若細菌突破初期防線，還有第二代的頭孢子菌素、aminoglycoside等著，第三線是超強的萬古黴素等抗生素。但現況是細菌抗藥性不斷增加，我們可以選擇的抗生素越來越少。

「這是醫院持續須面對的問題」，北市關渡醫院院長王聖賢表示，早年人類面對細菌束手無策，好不容易發明的抗生素又漸漸失效，他認為要從源頭管理，減少病菌傳播的機會，才能打贏這場人類與細菌的戰爭。

北醫大感染科主任李垣樟指出，現在綠膿桿菌、對萬古黴素產生抗藥性的金黃色葡萄球菌、一些結核菌，都出現幾乎百藥不入的「全抗藥性」變種，像金黃色葡萄球菌，是美國急診室現在最大的問題，因為它連最強的抗生素萬古黴素都能突破。

國衛院研究發現，全民健保使用的第一線抗生素如盤尼西林、健他黴素、紅黴素等，幾乎快要失效。新光醫院感染科醫師黃建賢也指出，雖然這兩年抗生素濫用的情況已獲注意，但院內感染目前至少要從第二線藥物開始嘗試，第一線藥物幾乎沒有防禦力。

感染科專家顏慕庸則表示，醫界對「全抗藥性」細菌，除了研發更新的抗生素，就是嘗試古老、已被遺忘的抗生素。這些古老的抗生素由於許久沒用，也許細菌對它已經不具有抗藥性，又有效了。

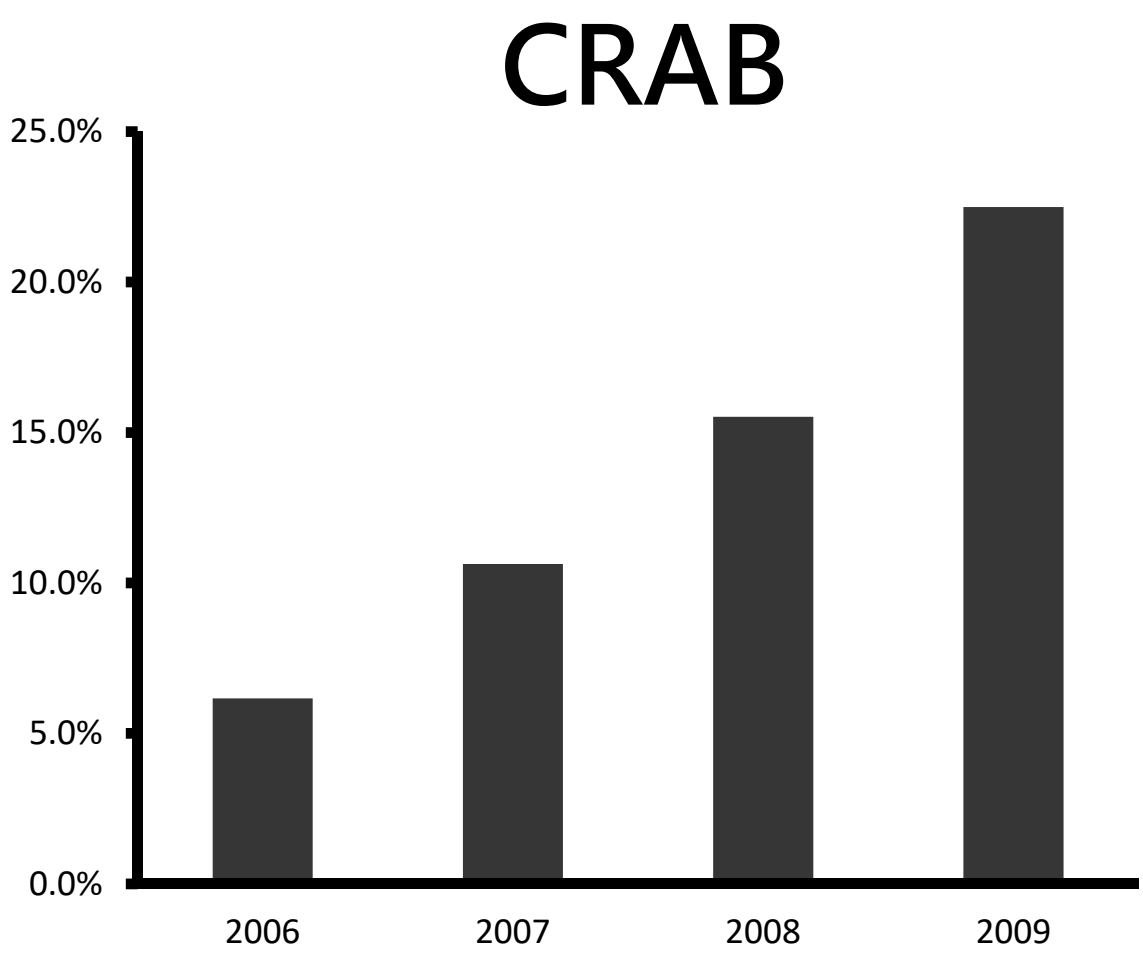
不過他認為，最好的方式還是從感染的源頭開始控制。「抗生素是萬靈丹的時代已經過去了，它變成是治療的末端」，顏慕庸說，加強院內洗手等清潔觀念、將感染的病患隔離避免造成更大規模的傳染，做好源頭管制是近十年醫界的體悟。

黃建賢也同意這樣的說法，「讓這些超級細菌困在醫院內，也許它們沒辦法擴張而自我淘汰」。

胡幼圃也建議，加強醫師給抗生素的訓練。他說，有些醫師給的劑量不足或時間不足，藥效不夠持久而產生抗藥性。顏慕庸說，有些醫師一看到感染就直接開最強的抗生素，結果細菌沒殺死，腸內的益菌反而被清光，讓出供超級細菌繁殖的空間。

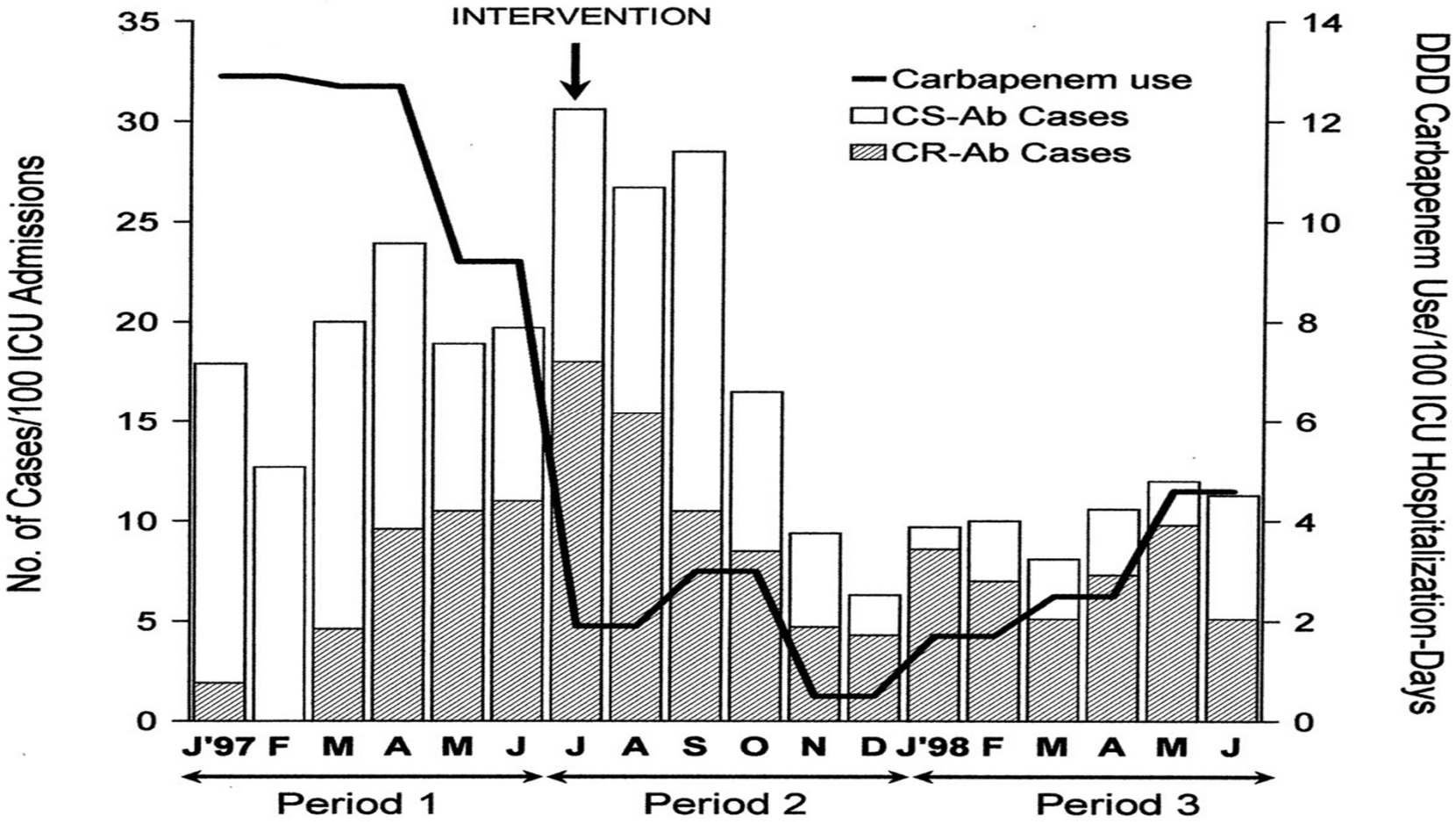
他認為，抗生素使用的種類、劑量、時間都是關鍵，正確地用抗生素，才能達到避免抗藥性細菌出現的效果。

CSMH Surveillance of Resistant Pathogens (2)



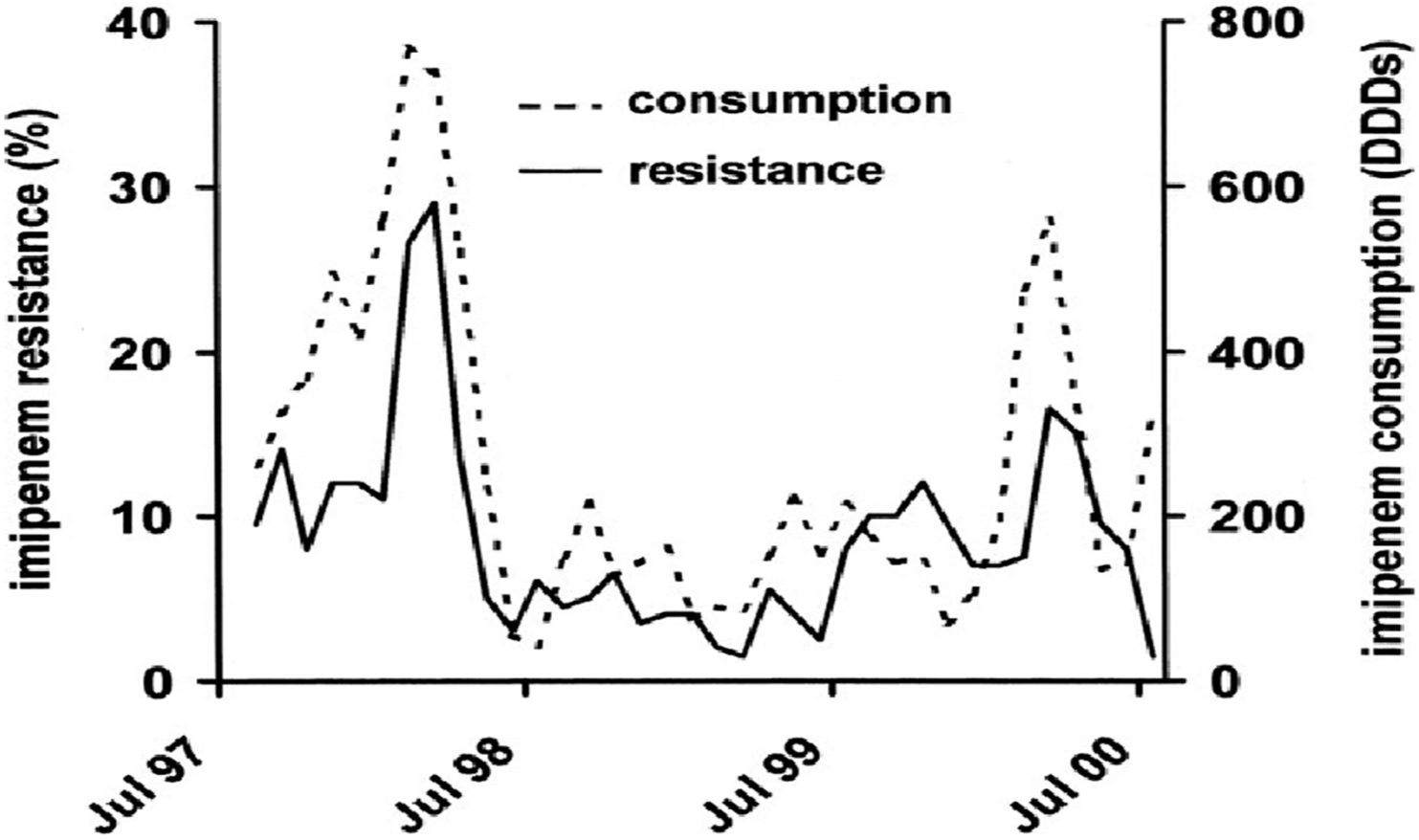
Imipenem Consumption *vs.* *Acinetobacter baumannii* Colonization/Infection

DDD = Defined daily doses of



Reprinted from Corbella X, et al. *J Clin Microbiol*. 2000;38:4086

Correlation Between Consumption of Imipenem and Resistance of *Pseudomonas aeruginosa*



Lepper PM, et al. *Antimicrob Agents Chemother*. 2002;46:2920

Bundles: CVC 2011~ VAP 2013~ CAUTI 2013~

CRAB感染治療的選擇: 現狀

- **Polymyxin E (Colistin)**
- **Polymyxin B**
- **Carbapenems**
- **Tigecycline**

Regimens

- **Monotherapy**
- **Combination therapy**

CRAB感染治療的選擇: 現狀

- **Polymyxin E (Colistin)**
- **Polymyxin B**

	• *Klebsiella pneumoniae* • *P. mirabilis*	diffusion	predicts results for the following oral antimicrobial agents: cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef Cefazolin as a surrogate may overcall resistance to cefdinir, cefpodoxime, and cefuroxime. If cefazolin tests resistant, test these drugs individually if needed for therapy.	
Cefoxitin	• *S. aureus* • *S. lugdunensis* • *S. epidermidis* • **Other *Staphylococcus* spp. (excluding *S. pseudintermedius* and *S. schleiferi*)**	Broth microdilution (*S. aureus* and *S. lugdunensis* only) or disk diffusion	Predicts results for *mecA*-mediated oxacillin resistance **NOTE: For *Staphylococcus* spp. other than *S. aureus, S. lugdunensis, S. epidermidis, S. pseudintermedius,* and *S. schleiferi,*** oxacillin MIC breakpoints may overcall resistance. Isolates for which the oxacillin MICs are 0.5–2 µg/mL have been shown to be *mecA* positive and *mecA* negative. Isolates from serious infections with MICs in this range may be tested for *mecA* or for PBP2a.	1A, 2C
Oxacillin	• *S. pneumoniae*	Disk diffusion	Predicts penicillin susceptibility if oxacillin zone is ≥20 mm. If oxacillin zone is ≤19 mm, penicillin MIC must be done.	1B, 2G
[illegible]	[illegible]	[illegible]	[illegible]	2A
Colistin	• ***Enterobacteriaceae*** • ***P. aeruginosa**** • ***A. baumannii* complex**	**Broth microdilution**	**MICs obtained from testing colistin predict MICs for polymyxin B.**	**2B-1, 2B-2, Appendix G**

2008 至2017 年醫學中心及區域醫院加護病房
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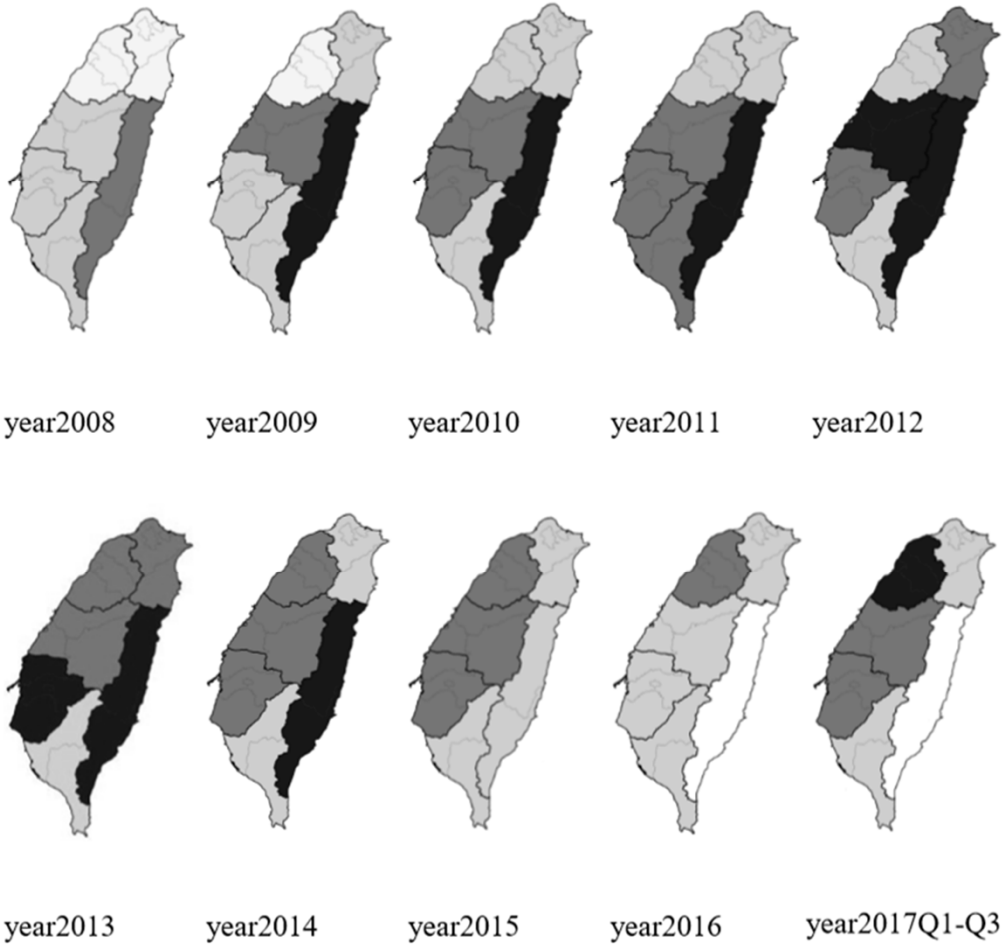
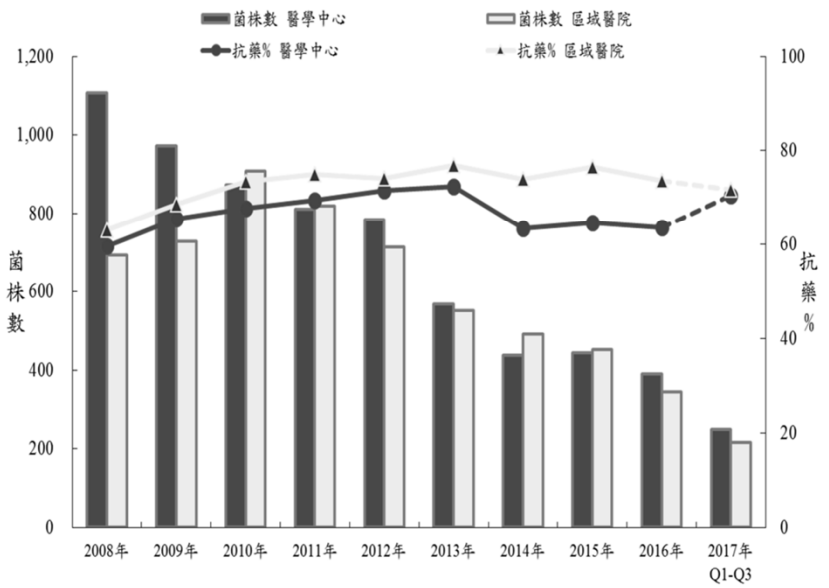
2008 至 2017 年第 3 季，區域級以上醫院加護病房醫療照護相關感染 CRAB 比率在 6 個區域的分布如圖 6。於 2008 年以東區(78.9%)較高；2017 年第 3 季 CRAB 比率以北區(84.7%)為最，中區(74.6%)次之。



CRAB

60%~80%

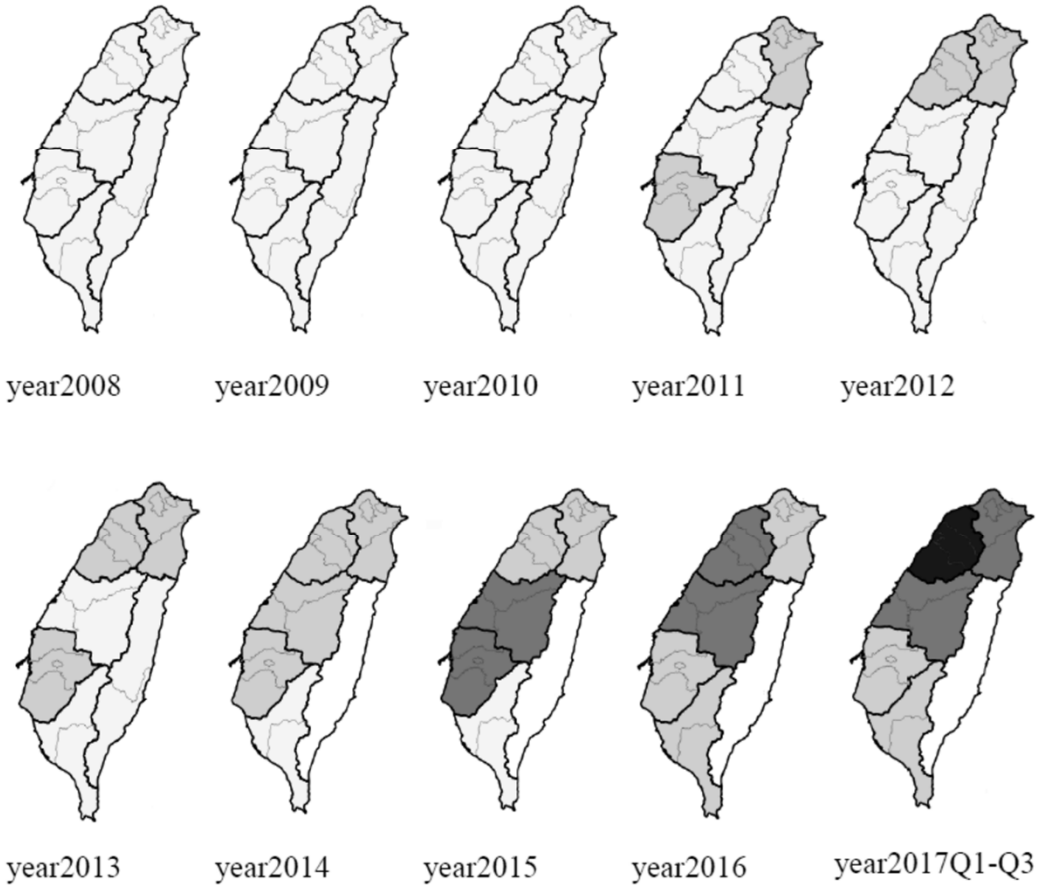


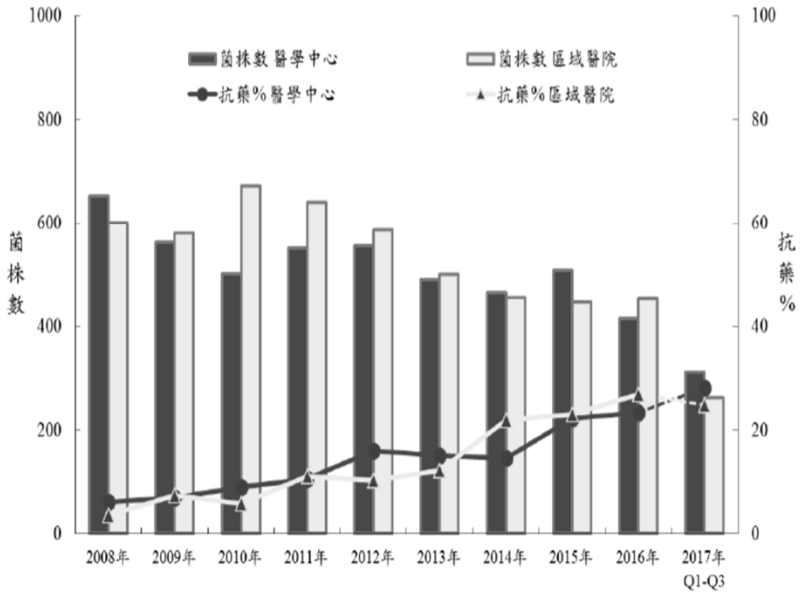
2008 至2017 年醫學中心及區域醫院加護病房
醫療照護相關感染CRKP百分比分佈圖

2008 至 2017 年第 3 季區域級以上醫院加護病房醫療照護相關感染 CRKP 比率在 6 區的分布如圖 12。於 2008 年以台北區(6.2%)較高；2017 年第 3 季 CRKP 比率以北區(48.1%)為最，台北區(28.9%)次之。

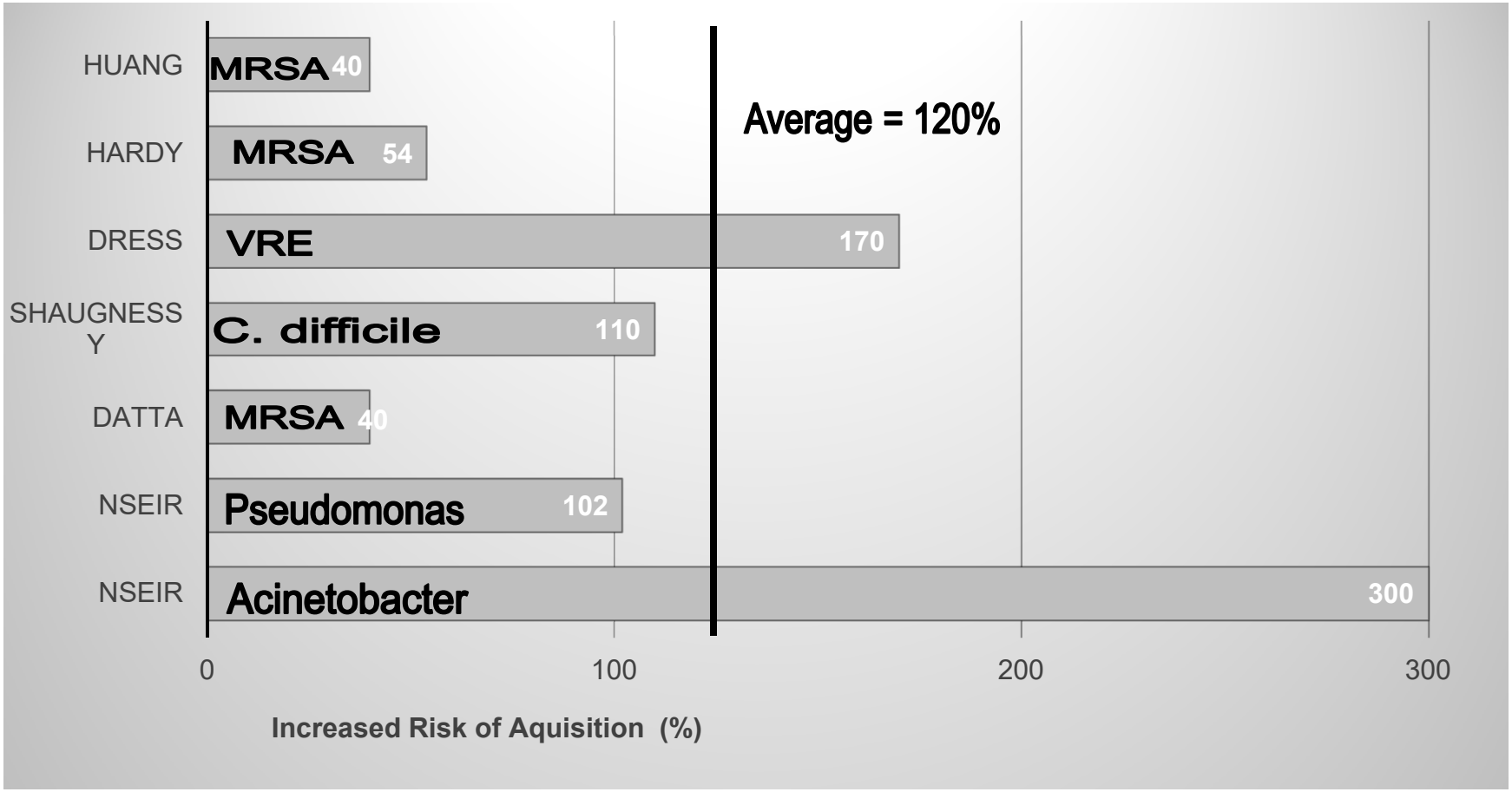
CRKP

達到 >30%



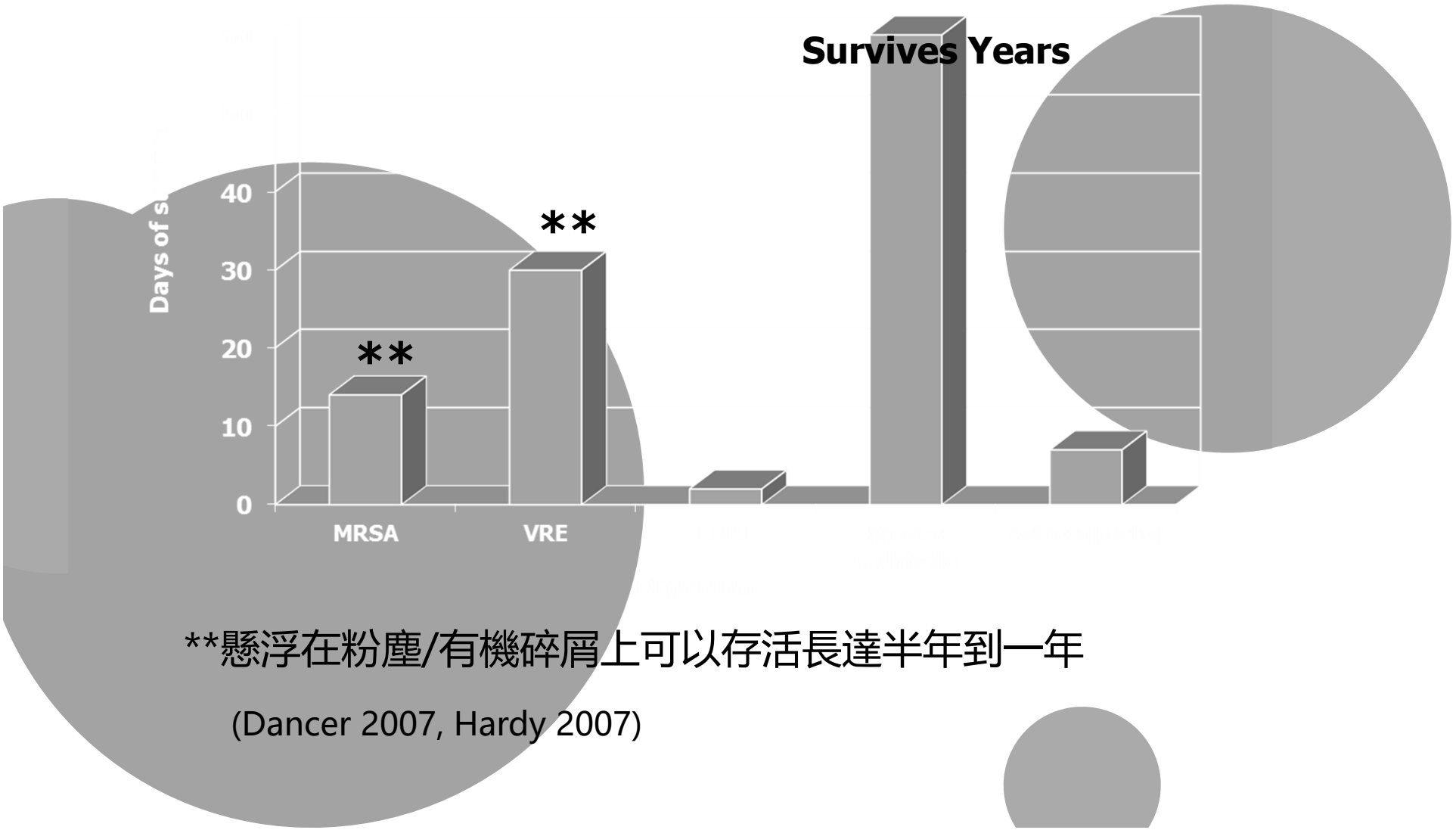


來自上一位住院者的合併風險
Increased acquisition risk from prior room occupant
6 studies as of January 2011



Carling PC, Bartley JM. Am J Infect Control 2010;38 S41-50.

無生物環境表面上的微生物存活



**懸浮在粉塵/有機碎屑上可以存活長達半年到一年

(Dancer 2007, Hardy 2007)

2008 至2017 年醫學中心及區域醫院加護病房
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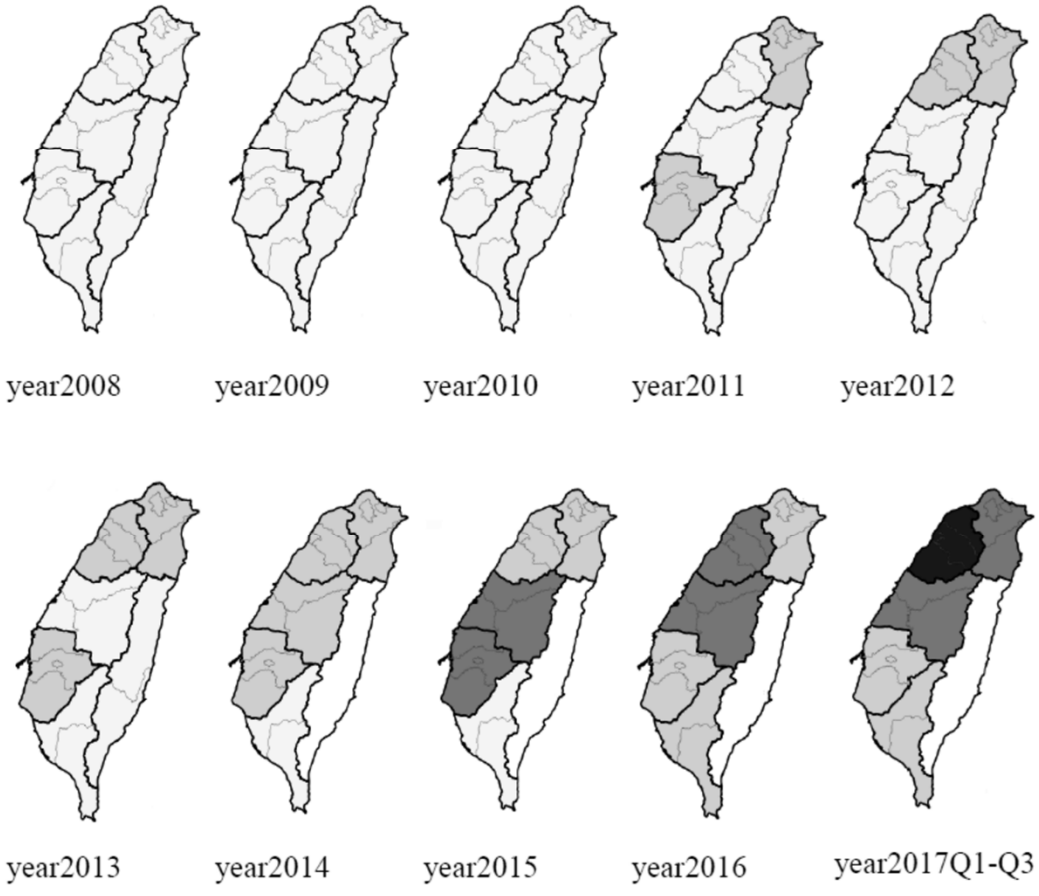
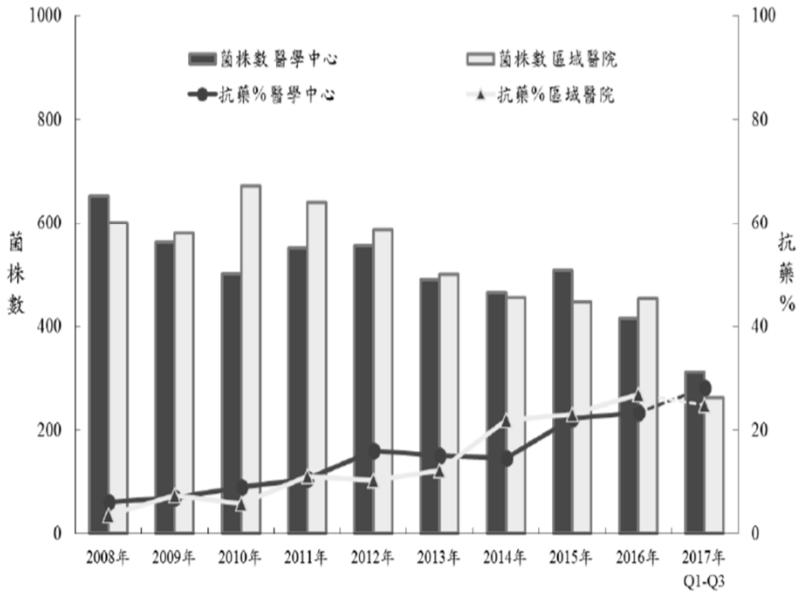
CRKP

達到 >30%

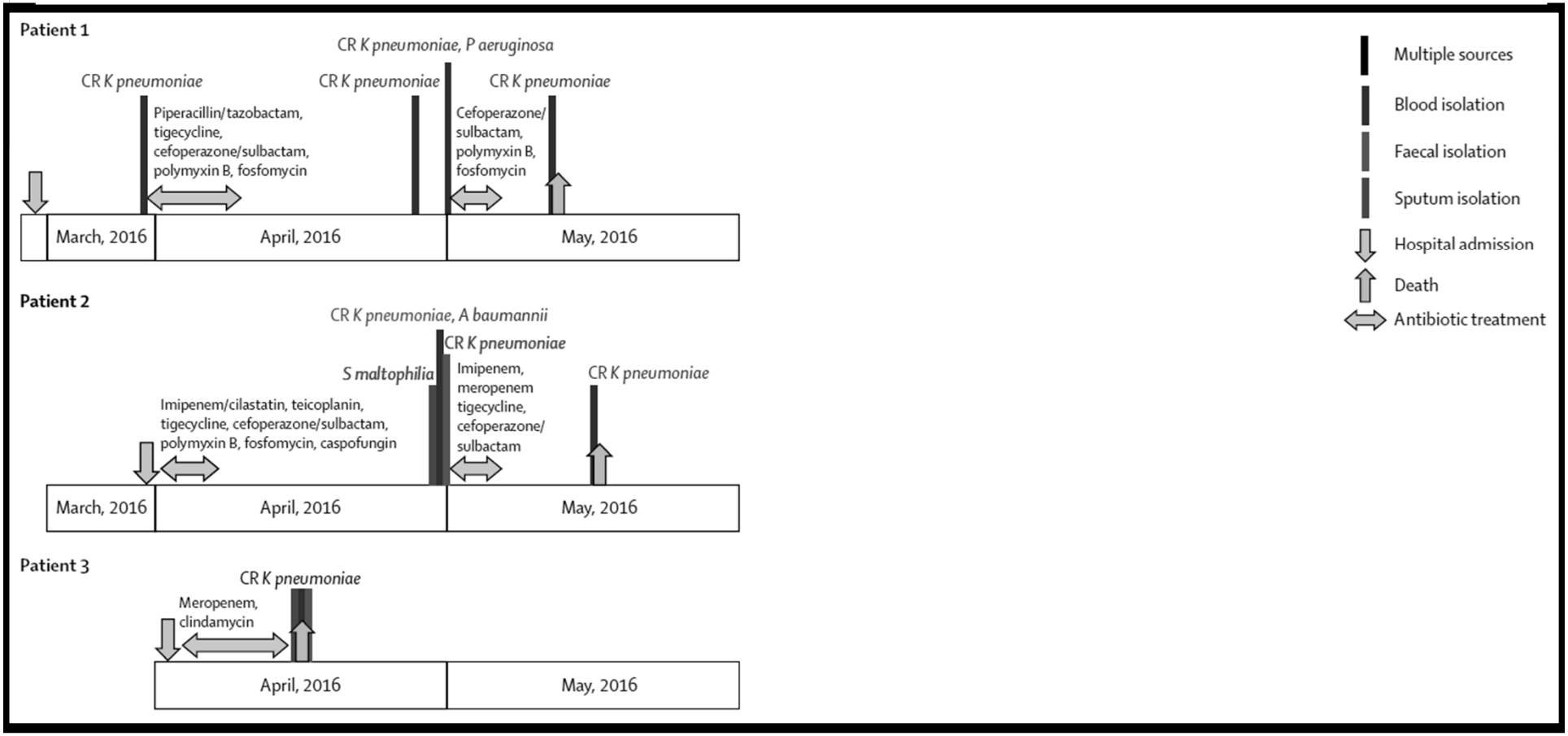




A fatal outbreak of ST11 carbapenem-resistant hypervirulent *Klebsiella pneumoniae* in a Chinese hospital: a molecular epidemiological study

Epidemiology of the *Klebsiella pneumoniae* outbreak cases

Danxia Gu, Ning Dong*, Zhiwei Zheng, Di Lin, Man Huang, Lihua Wang, Edward Wai-Chi Chan, Lingbin Shu, Jiang Yu, Rong Zhang, Sheng Chen*



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MLST type and antibiotic resistance characteristics of *Klebsiella pneumoniae* outbreak strains and their corresponding transconjugants

	Source of isolate	MLST	Antimicrobial resistance genes present	Minimum inhibitory concentration (μg/mL)												
				Imipenem	Ertapenem	Cefepime	Ceftriaxone	Cefazolin	Aztreonam	Amoxicillin plus clavulanic acid	Amikacin	Ciprofloxacin	Gentamicin	Tobramycin	Tigecycline	Piperacillin plus tazobactam
K pneumoniae 1	Patient 1	ST11	Yes	>16	>8	>64	>64	>64	>64	>32	>64	>4	>16	>16	0·5	>128
K pneumoniae 2	Patient 2	ST11	Yes	>16	>8	>64	>64	>64	>64	>32	>64	>4	>16	>16	0·5	>128
K pneumoniae 3	Patient 3	ST11	Yes	>16	>8	>64	>64	>64	>64	>32	>64	>4	>16	>16	1	>128
K pneumoniae 4	Patient 4	ST11	Yes	>16	>8	>64	>64	>64	>64	>32	>64	>4	>16	>16	0·5	>128
K pneumoniae 5	Patient 5	ST11	Yes	>16	>8	>64	>64	>64	>64	>32	>64	>4	>16	>16	0·5	>128

***Lancet Infect Dis* 2017** Published **Online** August 29, 2017
http://dx.doi.org/10.1016/S1473-3099(17)30489-9

Xu et al. Ann Clin Microbiol Antimicrob (2017) 16:18
DOI 10.1186/s12941-017-0191-3

Annals of Clinical Microbiology and Antimicrobials

RESEARCH Open Access

Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant *Klebsiella pneumoniae*

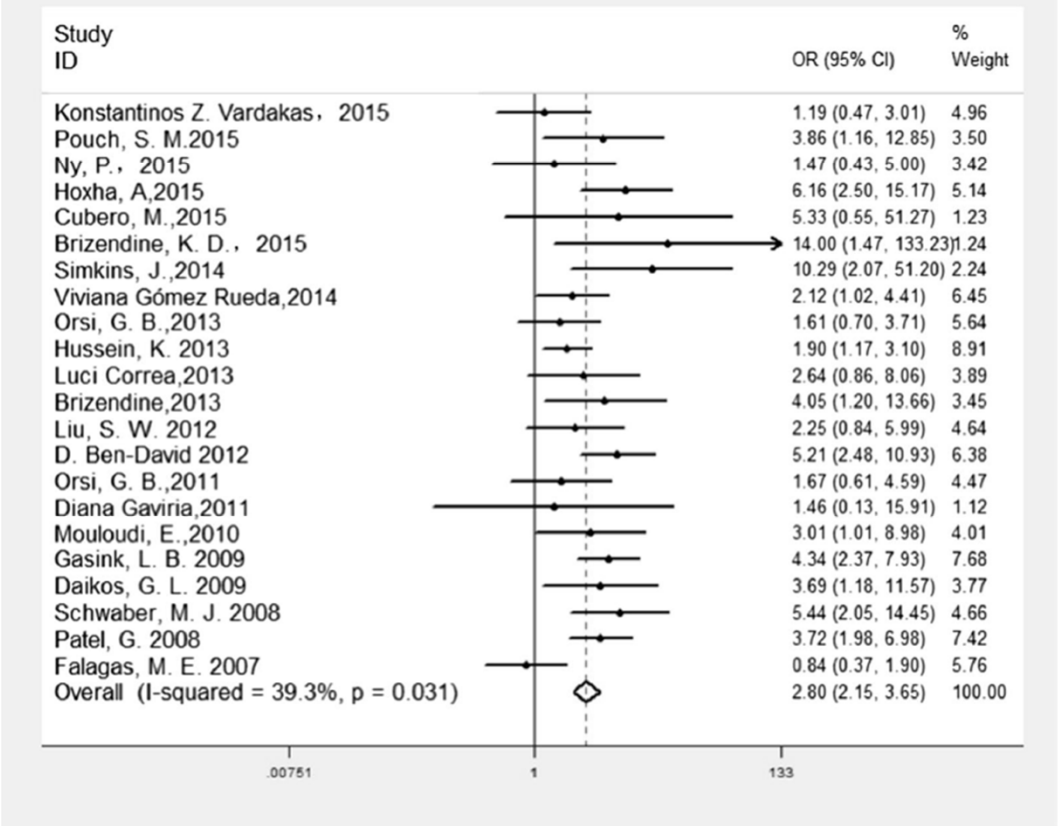


Fig. 2 Crude odds ratio (OR) for the association between carbapenem resistance and mortality of patients with *K. pneumoniae* infection

Xu et al. Ann Clin Microbiol Antimicrob (2017) 16:18
DOI 10.1186/s12941-017-0191-3

Annals of Clinical Microbiology and Antimicrobials

RESEARCH Open Access

Systematic review and meta-analysis of mortality of patients infected

Table 2 Mortality of patients based on patient condition, carbapenemases type, study region

Subgroup	Number of studies	Sample size	Mortality Rate %(95% CI)	Statistical model
Pooled mortality	P < 0.001			
CRKP	62	2462	42.14 (37.06–47.31)	Random
CSKP	22	2239	21.12 (16.07–26.79)	Random
Patient conditions	P < 0.001			
Bloodstream infections	20	722	54.30 (47.51–61.02)	Random
Urinary tract infections	8	284	13.52 (7.50–20.92)	Random
Intensive care unit	12	479	53.90 (39.44–68.00)	Random
Solid organ transplantation	15	362	43.13 (32.40–54.16)	Random
Carbapenemases type	P = 0.645			
KPC-producing *Klebsiella pneumoniae*	13	302	47.66 (38.61–49.51)	Random
VIM-producing *Klebsiella pneumoniae*	5	73	46.71 (35.81–57.73)	Random
Region	P = 0.062			
North America	23	980	33.24 (25.08–42.00)	Random
South America	8	191	46.71 (39.83–53.66)	Fixed
Europe	21	860	50.06 (41.45–58.62)	Random
Asia	10	431	44.82 (37.83–51.91)	Random

CRKP Carbapenem-resistant *K. pneumoniae*, *CSKP* carbapenem-susceptible *K. pneumonia*

Outbreak of *Klebsiella pneumoniae* Carbapenemase-2-Producing *K. pneumoniae* Sequence Type 11 in Taiwan in 2011

Chun-Ming Lee,[a,b,c] Chun-Hsing Liao,[d] Wen-Sen Lee,[e] Yung-Ching Liu,[f] Jung-Jung Mu,[g] Meng-Chih Lee,[a,h,i] and Po-Ren Hsueh[j]

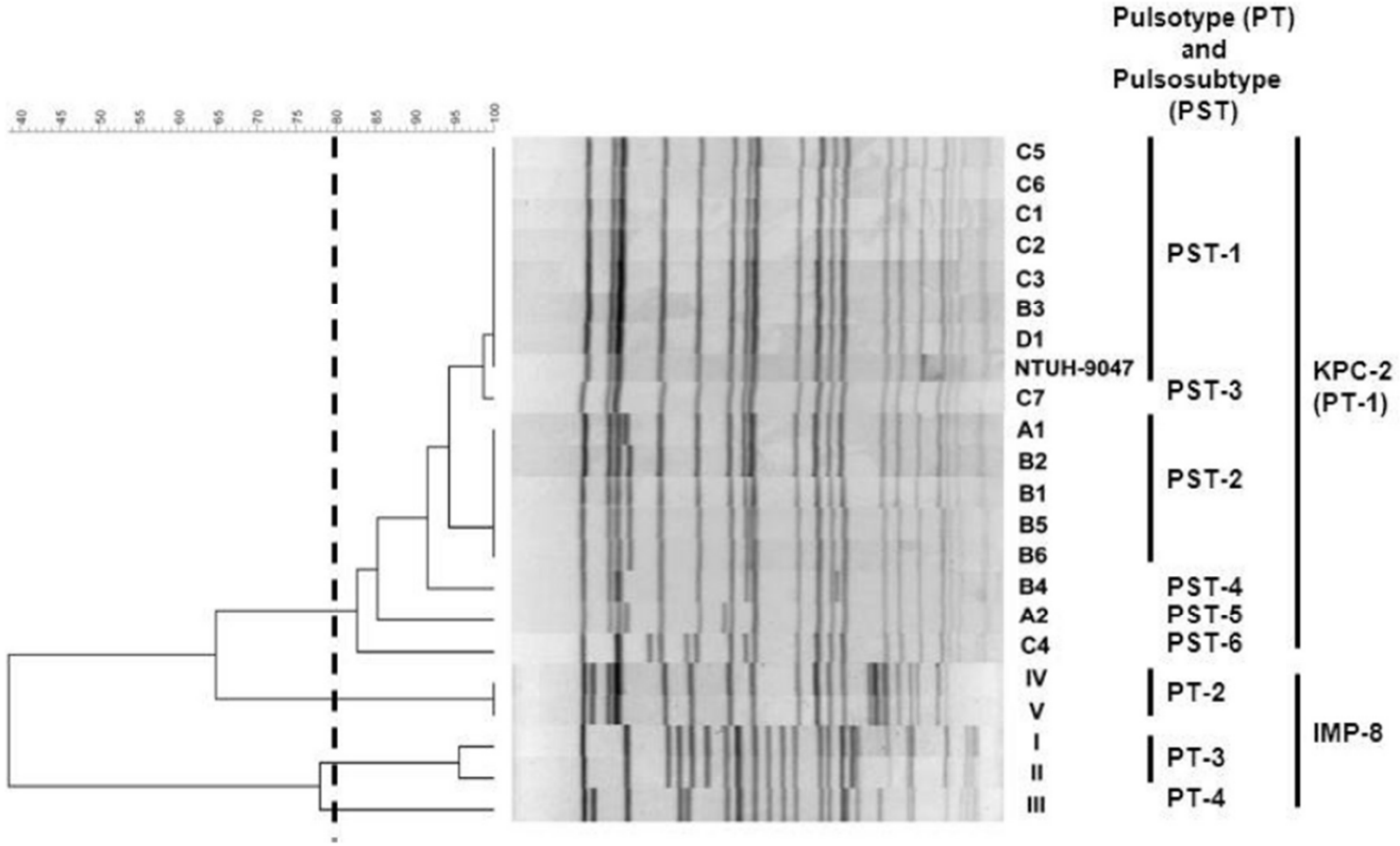


FIG 1 Pulsed-field gel electrophoresis profiles and dendrogram of the 16 KPC-2-KP isolates, 1 KPC-2-KP isolate previously reported (NTUH-9024) (10), and 5 IMP-8-producing *K. pneumoniae* isolates in Taiwan in 2011. See Tables 2 and 3 for isolate designations and the sources of the isolates.

Antimicrobial Agents and Chemotherapy 2012;56:5016

Emergence of OXA-48-Producing *Klebsiella pneumoniae* in Taiwan

Ling Ma[1], Jann-Tay Wang[2], Tsu-Lan Wu[3], L. Kristopher Siu[1], Yin-Ching Chuang[4,5], Jung-Chung Lin[6], Min-Chi Lu[7]*, Po-Liang Lu[8,9]*

PLOS ONE | DOI:10.1371/journal.pone.0139152 September 28, 2015

Table 1. Genetic features of four *bla*$_{OXA-48}$ *Klebsiella pneumoniae*.

Isolate	Specimen	β-lactam MICs (μg/mL)					ST type	Non-β-lactamassociated resistance	Associated β-lactamases	Inc
		ERT	IMP	MEM	CAZ	CTX				
1	sputum	≥8	≥8	≥8	≥32	≥64	11	Gm, Ak, Q, SXT	CTX-M-14, TEM-31, SHV-11	IncA/C
2	urine	≥8	≥8	≥8	16	≥64	11	Gm, Ak, Q, SXT	CTX-M-14, TEM-31, SHV-11	IncA/C
3	urine	≥8	≥8	≥8	≥32	≥64	11	Gm, Ak, Q, SXT, Cs	CTX-M-15, TEM-1, SHV-11	IncA/C
4	urine	≥8	≥8	4	≤1	≤1	116	none	SHV-1	NT

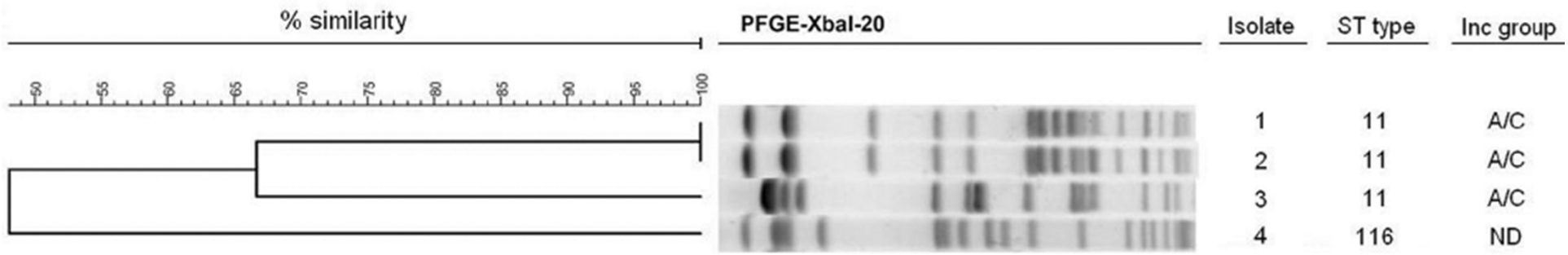


Fig 2. Dendrogram of XbaI-digested genomic DNA of four OXA-48 producing *Klebsiella pneumoniae* isolates.

Emergence of OXA-48-Producing *Klebsiella pneumoniae* in Taiwan

Ling Ma[1], Jann-Tay Wang[2], Tsu-Lan Wu[3], L. Kristopher Siu[1], Yin-Ching Chuang[4,5], Jung-Chung Lin[6], Min-Chi Lu[7]*, Po-Liang Lu[8,9]*

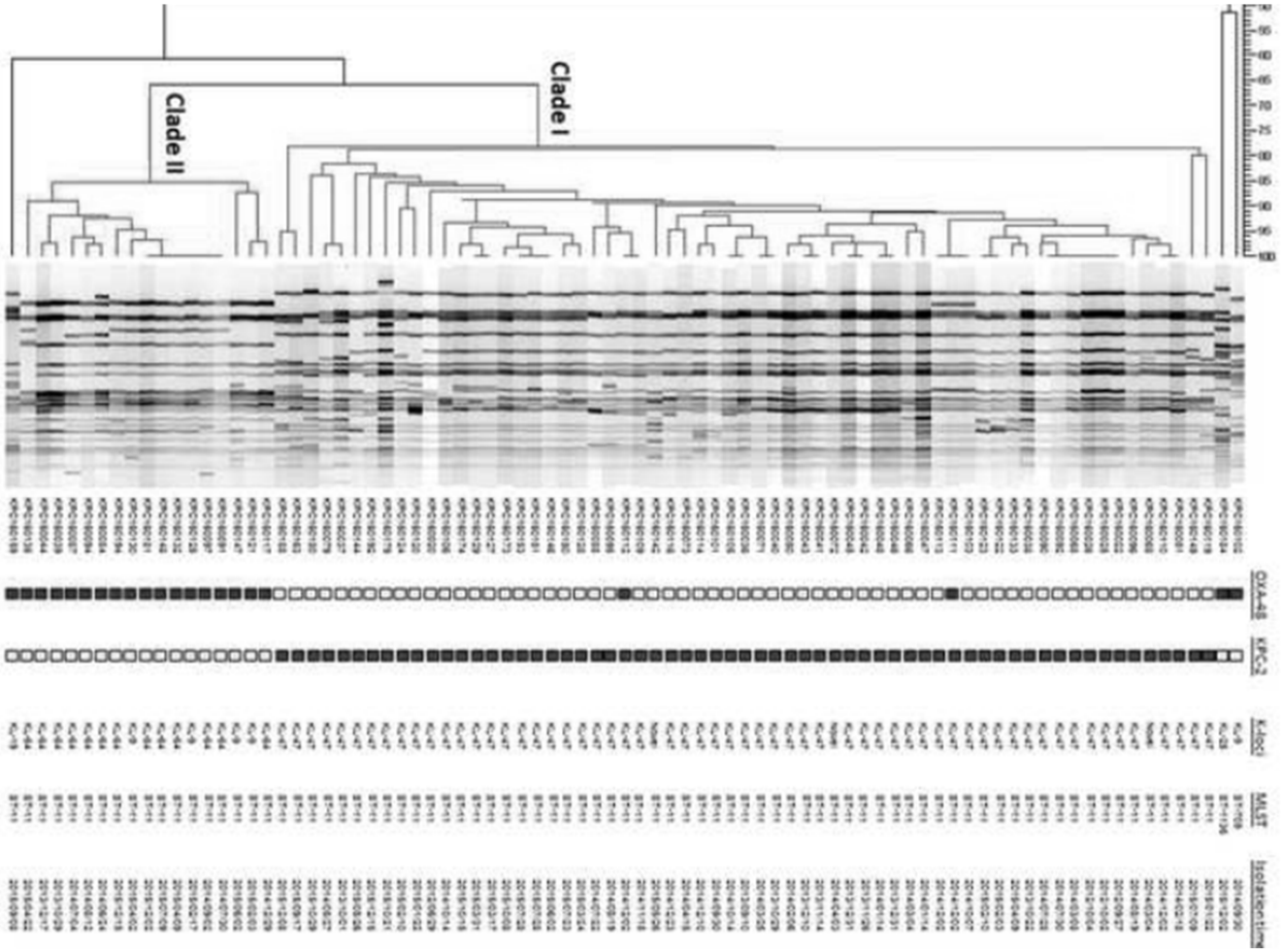
PLOS ONE | DOI:10.1371/journal.pone.0139152 September 28, 2015

- 在2012年1月至2014年5月，共收集到760株碳青黴烯類非敏感Klebsiella pneumoniae（CNSKP）菌株
- 在210株CNSKP分離株中檢出Carbapenemases（27.6%），其中162 kPC-2、KPC-3、KPC-17、NDM-1（n = 1）、OXA-48（n = 4）、IMP-8（n = 18）和VIM-1（n = 24）
- PFGE分析顯示，4個菌株屬於3個不同的脈衝型(PFGE type)。三個菌株擁有BLACTX-M基因，屬於MLST型ST11。此外，質粒(plasmid)屬於不相同組，IncA / C。一個屬ST116，而質粒不相同組不可分型
- 這是臺灣產OXA-48產腸桿菌科細菌的首次報告，在K. pneumoniae的**IncA/C**質粒上鑒定blaOXA-48的第一個報告

Article in Press

Clonal dissemination of carbapenemase-producing *Klebsiella pneumoniae*: Two distinct sub-lineages of Sequence Type 11 carrying bla_{KPC-2} and bla_{OXA-48}

Min-Chi Lu, Hui-Ling Tang, Chien-Shun Chiou, Yao-Chen Wang, Ming-Ko Chiang, Yi-Chyi Lai



Int J Antimicrob Agents. 2018 May 9. pii: S0924-8579(18)30132-8.

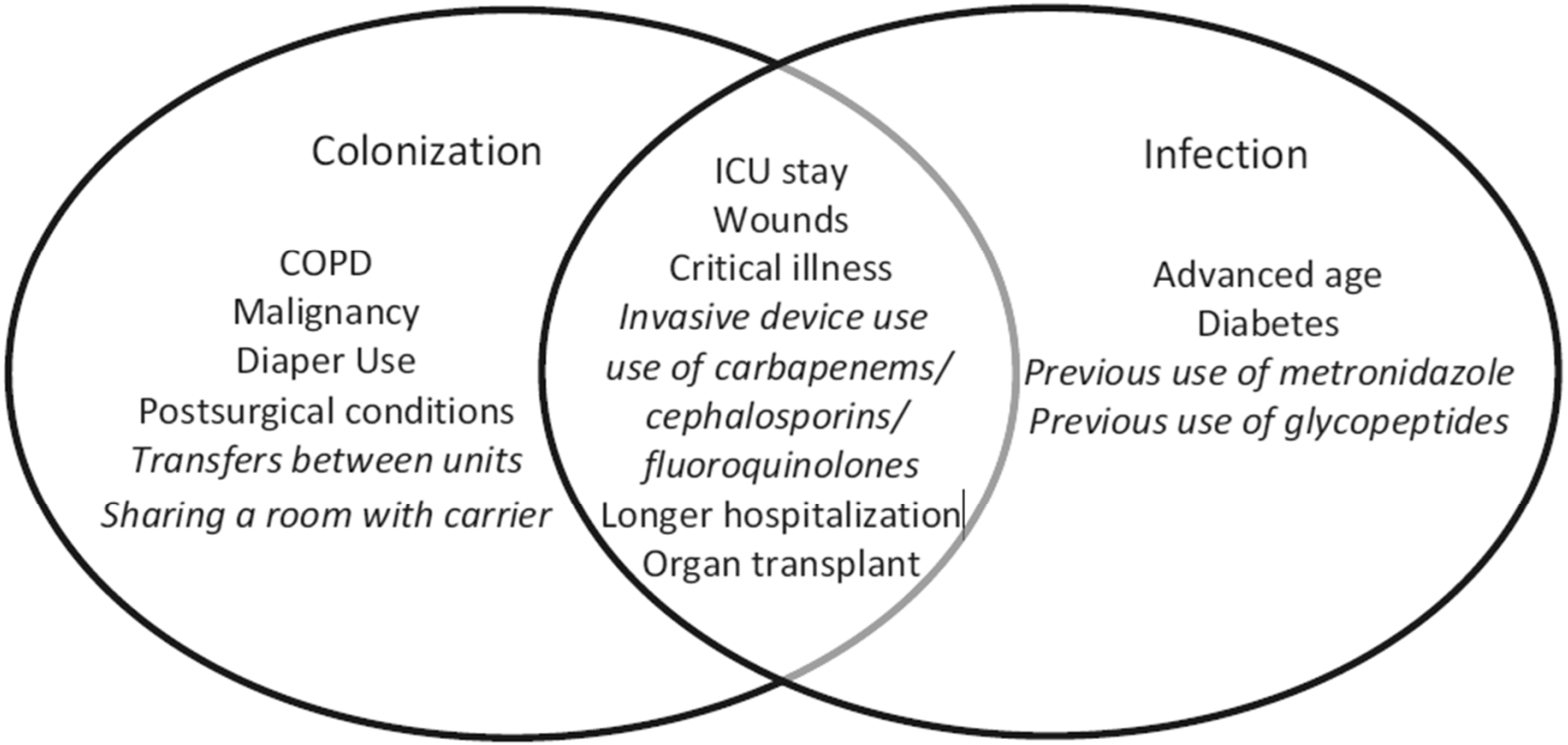
Table 2. *In vitro* activities of the antimicrobial agents tested against carbapenem-resistant *K. pneumoniae* strains.

Antimicrobial agent	KPC-2 (*n*=63)			OXA-48 (*n*=22)			Other (*n*=91)		
	[a]MIC_{50}	[b]MIC_{90}	[c]S (%)	[a]MIC_{50}	[b]MIC_{90}	[c]S (%)	[a]MIC_{50}	[b]MIC_{90}	[c]S (%)
Amikacin	≤8	>32	68.3	>32	>32	40.9	≤8	>32	64.8
Gentamicin	>8	>8	41.3	>8	>8	36.4	>8	>8	32.9
Ertapenem	>4	>4	0	>4	>4	0	>4	>4	0
Meropenem	>8	>8	0	4	>8	31.8	2	8	61.5
Imipenem	>8	>8	0	8	>8	27.3	4	>8	36.3
Ciprofloxacin	>2	>2	0	>2	>2	0	>2	>2	13.2
Levofloxacin	>4	>4	0	>4	>4	4.5	>4	>4	22.0
Cefazolin	>16	>16	0	>16	>16	0	>16	>16	0
Ceftazidime	>16	>16	0	>16	>16	4.5	>16	>16	1.1
Ceftriaxone	>32	>32	0	>32	>32	9.1	>32	>32	8.8
Cefepime	>16	>16	0	>16	>16	4.5	>16	>16	14.3
Trimethoprim/ Sulfamethoxazole	>2/38	>2/38	15.9	>2/38	>2/38	18.2	>2/38	>2/38	20.9
Piperacillin/ Tazobactam	>64/4	>64/4	0	>64/4	>64/4	0	>64/4	>64/4	4.4
Ampicillin/ Sulbactam	>16/8	>16/8	0	>16/8	>16/8	0	>16/8	>16/8	0

MIC: minimal inhibitory concentration. [a]MIC_{50}: MIC for 50% of strains. [b]MIC_{90}: MIC for 90% of strains. [c]S (%): Percentage of strains susceptible to an antimicrobial agent.

J Antimicrob Agents. 2018 May
pii: S0924-8579(18)30132-8.

碳青黴烯類抗藥的腸桿菌科細菌:
定植、感染或兩者相關的危險因素



斜體字可以通過適當的感染控制或抗菌管理來預防

Clin Microbiol Infect 2014; 20: 854–861

CRE 感染治療的選擇: 現狀

- Colistin (polymyxin E)
- Polymyxin B
- Carbapenems
- **Tigecycline**
- Fosfomycin

Regimens

- **Monotherapy**
- **Combination therapy**
  - Carbapenem-based regimen
  - **Double carbapenem (doripenem + ertapenem) regimen**
  - **Tigecycline-based (Carbapenem sparing) regimen**
- New drug

Preva…olecular epide…cteriaceae in patie…n epidemiological and c…

Lancet Infect Dis 2017;17: 390–99

Yang Wang, … Zhou, Lei Lei, Hong-Yu Li, Yohei Doi, Ying Fan Hongwei Ren … g Wu, Timothy R Walsh, Jianzhong Shen*

	mcr-1-negative *E coli* (n=508)	*mcr-1*-positive *E coli* (n=76)	p value
Colistin	53/455 (10%)	74/2 (97%)	<0·0001
Polymyxin B	117/391 (23%)	74/2 (97%)	<0·0001
Tigecycline	24/467 (5%)	1/71 (1%)	0·178
Ampicillin	442/66 (87%)	72/4 (95%)	0·053
Amoxicillin plus clavulanic acid	125/383 (25%)	45/31 (59%)	0·0005
Cefotaxime	292/200 (58%)	64/10 (84%)	0·0005
Ceftazidime	172/260 (34%)	41/24 (54%)	0·0008
Cefepime	185/219 (36%)	43/21 (57%)	0·001
Gentamicin	227/277 (45%)	46/25 (61%)	0·002
Amikacin	12/490 (2%)	14/60 (18%)	<0·0001
Ertapenem	12/490 (2%)	5/70 (7%)	0·041
Imipenem	4/504 (1%)	1/75 (1%)	0·641
Meropenem	1/501 (<1%)	0/75	0·699
Fosfomycin	182/326 (36%)	45/31 (59%)	0·0008
Nitrofurantoin	11/497 (2%)	7/69 (9%)	0·0009
Ciprofloxacin	313/175 (62%)	62/11 (82%)	0·0005

Data are number resistant/number sensitive (% of resistance rates). p value for comparisons of the resistance rates of *mcr-1*-positive and *mcr-1*-negative groups.

Table 1: **Minimum inhibitory concentration profiles of clinical infection-derived *Escherichia coli* with or without *mcr-1***

多藥抗藥陰性菌MDR-GNB的新藥

β-lactam Combination Agents

Ceftazidime-avibactam
Ceftolozane-tazobactam
Cefepime-tazobactam
Aztreonam-avibactam
Ceftaroline-avibactam
Imipenem-relebactam
Meropenem-vaborbactam
Cefepime-zidebactam
Meropenem-nacubactam

Non-β-lactam Agents

Cefiderocol
Murepavadin
Finafloxacin
Eravacycline
Omadacycline
Plazomicin
Delafloxacin

Avery LM & Nicolau DP. *Expert Opinion on Investigational Drugs* 2018;27:4:325-38.

β型內醯胺酶抑制劑對不同β型內醯胺酶活性的影響

β-lactamase inhibitor

	Avibactam/ Relebactam	Vaborbactam	Zidebactam/V NRX-5133	Nacubactam	Sulbactam/ clavunlanate	Tazobactam
Class A						
TEM	+	+	+	+	+/+	+
SHV	+	+	+	+	+/+	+
CTX-M	+	+	+	+	+/+	+
KPC	+	+	+	+[m]	-/-	-
Class B						
MBL	-	-	+	-	-	-
Class C						
AmpC	+	+	+	+	-/±[a]	+
Class D						
OXA	±(OXA-48)	-[b]	+	+w	-/-	-

[a]Enterobacteriaceae resist inhibition by sulbactam, although *Klebsiella* spp., *Salmonella* spp., and *Proteus* spp. normally do not harbor chromosomal bla_{AmpC} genes

[b] Limited data available

Zhanel GG et al. *Drugs* 2018;78:65-98.

新型抗生素對VAP的MDR-GNB活性譜

Agent	ESBL	KPC	OXA-48	MBL	MDR-PA	MDR-AB
Ceftolozane-tazobactam	ν				ν	
Ceftazidime-avibactam	ν	ν	ν			
Ceftaroline-avibactam	ν	ν	ν			
Aztreonam-avibactam	ν	ν	ν	ν		
Imipenem-relebactam	ν	ν				
Meropenem-vaborbactam	ν	ν				
Cefiderocol	ν	ν	ν	ν	ν	ν
Plazomicin	ν	ν	ν	ν[a]	ν	
Eravacyclin	ν	ν	ν	ν		ν
Murepavadin					ν	

[a]Not active against many NDMs

Bassetti M et al. *Curr Opin Infect Dis* 2018;31:177-186.

Ceftolozane–tazobactam

- 以ESBL和*P. aeruginosa*為治療的目標
  - 克服抗藥機制（如AmpC、外膜蛋白損失和外排泵的上調）
  - 對碳青黴烯類耐藥菌株不產生碳青黴烯酶的有效活性
  - 治療目標為cIAI和cUT
- 21例MDR-*P aeruginosa*感染
  - 71%成功
  - 體內抗藥性14%
- 治療VAP的免除碳青黴烯類藥物方案 (carbapenem-sparing regimen)

Bassetti M et al. *Curr Opin Infect Dis* 2018;31:177-186.

Ceftazidime-avibactam

- cIAI and cUTIs
  - 比較Meropenem或Imipenem的治療為非劣效性
  - CAZ-R與BAT：cUTI（91.7%比94.2%）和cIAI（80%比54.5%）與BAT
- REPROVE研究綜述
  - Ceftazidime-avibactam (n = 356) 和Meropenem (n = 370)
  - 非劣效性結果： Ceftazidime-avibactam 68.8%Meropenem72.9%
  - VAP cohort中的成功率相似
- CRE感染
  - 總成功率45-76%
- 治療肺炎的 carbapenem-sparing regimen
  - 結合gentamycin, fosfomycin, colistin, or plazomycin

Bassetti M et al. *Curr Opin Infect Dis* 2018;31:177-186.
Sharma R et al. *Clinical Therapeutics* 2016;38:431-44.

Activity of plazomicin compared with other aminoglycosides against isolates from European and adjacent countries, including Enterobacteriaceae molecularly characterized for aminoglycoside-modifying enzymes and other resistance mechanisms

Table 2. Activity of plazomicin and comparators tested against clinical isolates collected in European and adjacent countries during 2014 and 2015

	Percentage inhibited by plazomicin at		Percentage susceptible applying EUCAST breakpoints						
Organism/organism group (no. of isolates)	2 mg/L	4 mg/L	amikacin	gentamicin	meropenem	piperacillin/ tazobactam	levofloxacin	tigecycline	colistin
Enterobacteriaceae (4217)	95.8	98.0	94.1	84.3	94.8	78.2	72.1	95.3	83.8
CRE (227)	84.6	84.6	33.9	43.6	4.0	0.0	5.3	88.9	65.9
Isolates carrying bla_{KPC} (113)	92.9	92.9	22.1	71.7	4.4	0.0	2.7	89.3	65.2
Isolates carrying MBL genes (37)	42.1	42.1	13.5	21.6	5.4	0.0	16.2	83.8	78.4
Isolates carrying bla_{OXA-48}-like (54)	87.0	87.0	68.5	20.4	25.9	0.0	11.1	94.4	59.3
Carbapenemase-negative isolates (59)	94.9	94.9	64.4	28.8	37.3	6.8	18.6	91.5	81.4
Isolates carrying AME genes (728)	99.0	99.3	76.9	31.3	78.2	36.3	17.9	94.6	87.0
Isolates carrying 16S rRNA methyltransferase genes (60)	0.0	0.0	0.0	0.0	46.7	15.0	10.0	86.7	83.1
P. aeruginosa (102)	32.4	75.5	88.2	87.3	79.4	80.2	70.6	NI	100.0
Acinetobacter spp. (99)	40.4	45.5	34.3	41.4	41.4	NI	31.3	NI	89.9

J Antimicrob Chemother doi:10.1093/jac/dky344

醫院環境的環境污染是常見的

Environmental Contamination by Carbapenem-Resistant *Enterobacteriaceae*

A. Lerner, A. Adler, J. Abu-Hanna, I. Meitus, S. Navon-Venezia, Y. Carmeli

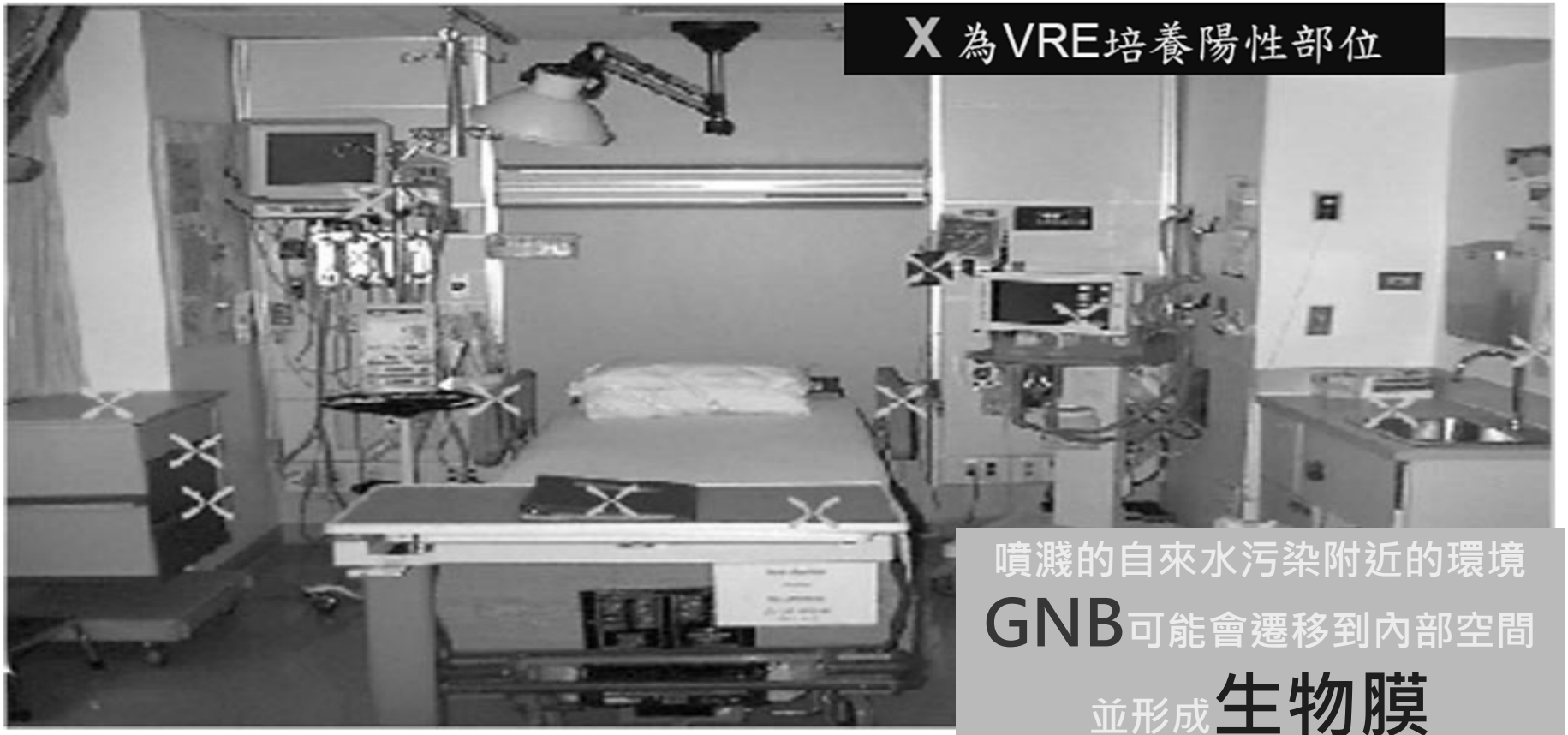
Division of Epidemiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

In the last decade, the global emergence of carbapenem resistance in *Enterobacteriaceae* has posed great concern to public health. Data concerning the role of environmental contamination in the dissemination of carbapenem-resistant *Enterobacteriaceae* (CRE) are currently lacking. Here, we aimed to examine the extent of CRE contamination in various sites in the immediate surroundings of CRE carriers and to assess the effects of sampling time and cleaning regimens on the recovery rate. We evaluated the performance of two sampling methods, CHROMAgar KPC contact plate and eSwab, for the detection of environmental CRE. eSwab was followed either by direct plating or by broth enrichment. First, 14 sites in the close vicinity of the carrier were evaluated for environmental contamination, and 5, which were found to be contaminated, were further studied. The environmental contamination decreased with distance from the patient; the bed area was the most contaminated site. Additionally, we found that the sampling time and the cleaning regimen were critical factors affecting the prevalence of environmental CRE contamination. We found that the CHROMAgar KPC contact plate method was a more effective technique for detecting environmental CRE than were eSwab-based methods. In summary, our study demonstrated that the vicinity of patients colonized with CRE is often contaminated by these organisms. Using selective contact plates to detect environmental contamination may guide cleaning efficacy and assist with outbreak investigation in an effort to limit the spread of CRE.

Lerner, J Clin Microbiol 2013

醫院環境哪裡有多重耐藥性菌種？

藉由人的雙手污染環境



噴濺的自來水污染附近的環境

GNB可能會遷移到內部空間

並形成**生物膜**

~ 污染的環境表面增加交叉感染的機會 ~

The Risk of Hand and Glove Contamination after Contact with a VRE (+) Patient Environment. Hayden M, ICAAC, 2001, Chicago, IL.

VRE: vancomycin-resistant enterococci

醫院被污染的水槽

- 污染的洗手水槽被認定為CRE的持續傳播來源/貯存窩

Lowe, Infect Control Hosp Epidemiol 2013
Vergara-Lopez, Clin Microbiol Infect 2013
Leitner, Antimicrob Agents Chemother 2015

New Acquisition of Antibiotic-Resistant Organisms (ARO) in Skilled Nursing Facilities

Fisch J et al., JCM 50:1698, 2012

- A large prospective microbial study involving **15 SNFs located Michigan**
- 90 /178 residents had an **indwelling device** (a urinary catheter, feeding tube, or both). 82 residents (46%) qualified for this analysis (21 with device)
- To define the attributable fraction of device-associated infections and ARO colonization

TABLE 1 Baseline data for the 82 SNF residents enrolled in the study

Characteristic	Value for SNF residents: Without indwelling device ($n = 61$)	With indwelling device ($n = 21$)	P value
Age (yr, mean ± SD)	83.49 ± 9.85	77.52 ± 13.88	0.03
Wt (lb, mean ± SD)	157.46 ± 43.41	160.60 ± 46.12	0.78
No. (%) male	12 (20)	10 (48)	
No. (%) white	59 (97)	16 (76)	
Comorbidity score	2.25 ± 1.59	3.00 ± 1.52	0.06
PSMS	19.31 ± 5.19	24.00 ± 4.95	<0.01
Follow-up days in the study	278.36 ± 81.82	228.57 ± 95.57	0.02
Admission time in facility	39.10 ± 44.54	45.98 ± 101.23	0.67
No. (%) with:			
Prior hospitalization	7 (11)	12 (57)	<0.001
Antibiotic usage	43 (70)	17 (81)	0.35
Ciprofloxacin usage	12 (20)	4 (19)	0.95

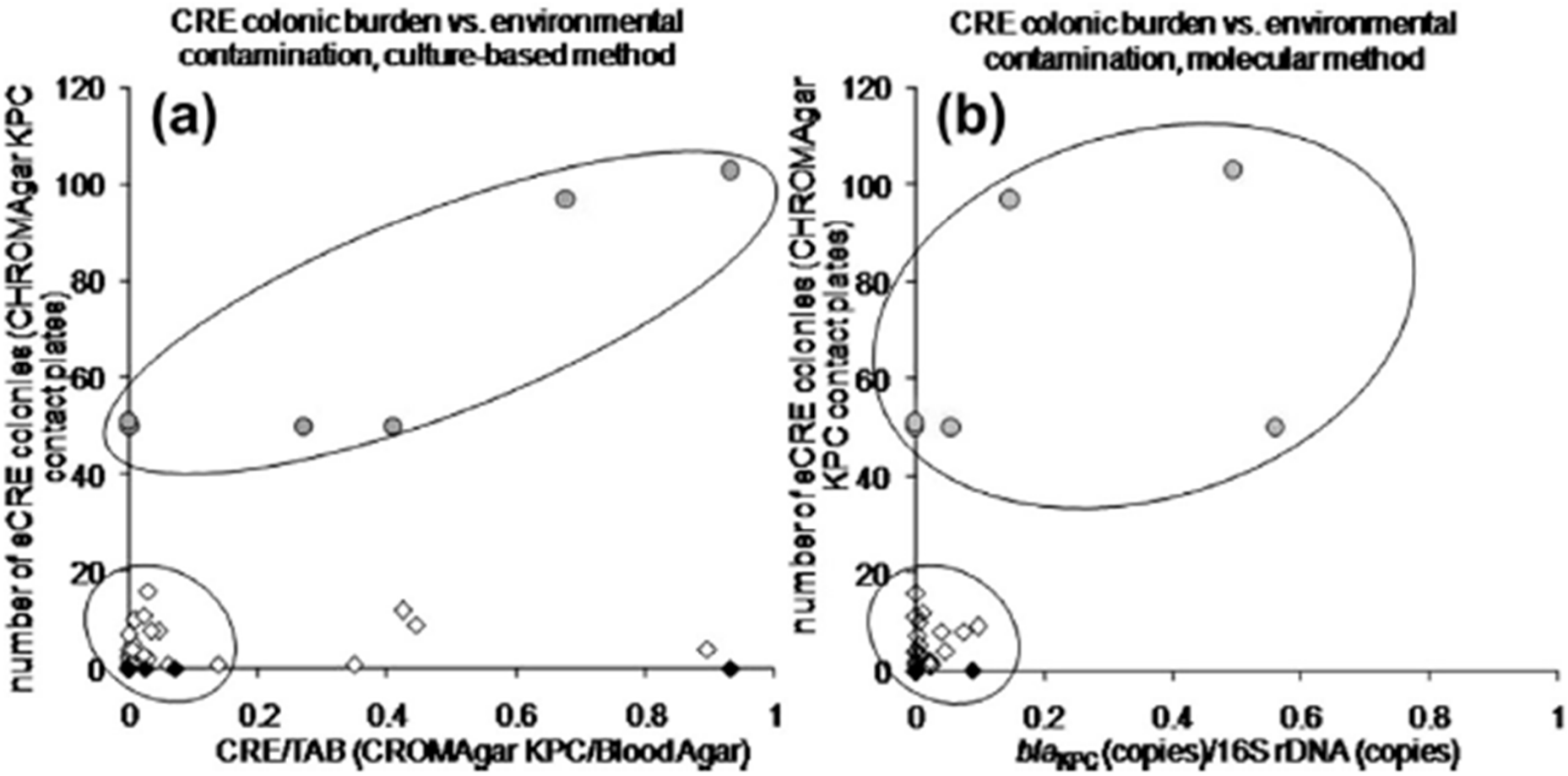
長照可以是MDRO的貯存窩?!

Spread of KPC-producing carbapenem-resistant Enterobacteriaceae: the importance of super-spreaders and rectal KPC concentration

A. Lerner, A. Adler, J. Abu-Hanna, S. Cohen Percia, M. Kazma Matalon and Y. Carmeli

Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel

CRE的超級傳染源



Clin Microbiol Infect 2015; 21: 470.e1–470.e7

CRE 糞便帶菌

- **CRE糞便帶菌的平均持續時間**
  - **出院後387天**
  - **出院1年：仍攜帶CRE比例 39%**
- **與延長帶菌相關的風險：**
  - **重複住院**
  - **由臨床培養的CRE（不只是篩選培養）**

Zimmerman, Am J Infect Control 2013

Research

Original Investigation

New Delhi Metallo-β-Lactamase–Producing Carbapenem-Resistant *Escherichia coli* Associated With Exposure to Duodenoscopes

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IMPORTANCE Carbapenem-resistant Enterobacteriaceae (CRE) producing the New Delhi metallo-β-lactamase (NDM) are rare in the United States, but have the potential to add to the increasing CRE burden. Previous NDM-producing CRE clusters have been attributed to person-to-person transmission in health care facilities.

OBJECTIVE To identify a source for, and interrupt transmission of, NDM-producing CRE in a northeastern Illinois hospital.

DESIGN, SETTING, AND PARTICIPANTS Outbreak investigation among 39 case patients at a tertiary care hospital in northeastern Illinois, including a case-control study, infection control assessment, and collection of environmental and device cultures; patient and environmental isolate relatedness was evaluated with pulsed-field gel electrophoresis (PFGE). Following identification of a likely source, targeted patient notification and CRE screening cultures were performed.

MAIN OUTCOMES AND MEASURES Association between exposure and acquisition of NDM-producing CRE; results of environmental cultures and organism typing.

RESULTS In total, 39 case patients were identified from January 2013 through December 2013, 35 with duodenoscope exposure in 1 hospital. No lapses in duodenoscope reprocessing were identified; however, NDM-producing *Escherichia coli* was recovered from a reprocessed duodenoscope and shared more than 92% similarity to all case patient isolates by PFGE. Based on the case-control study, case patients had significantly higher odds of being exposed to a duodenoscope (odds ratio [OR], 78 [95% CI, 6.0-1008], $P < .001$). After the hospital changed its reprocessing procedure from automated high-level disinfection with ortho-phthalaldehyde to gas sterilization with ethylene oxide, no additional case patients were identified.

CONCLUSIONS AND RELEVANCE In this investigation, exposure to duodenoscopes with bacterial contamination was associated with apparent transmission of NDM-producing *E coli* among patients at 1 hospital. Bacterial contamination of duodenoscopes appeared to persist despite the absence of recognized reprocessing lapses. Facilities should be aware of the potential for transmission of bacteria including antimicrobial-resistant organisms via this route and should conduct regular reviews of their duodenoscope reprocessing procedures to ensure optimal manual cleaning and disinfection.

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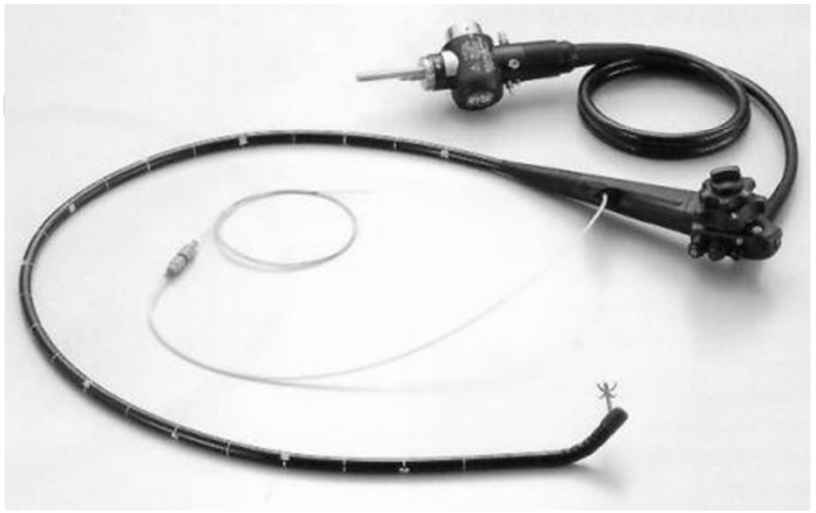
CRE 可經由十二指腸內視鏡 Duodenescopes散播



CRE 可經由ERCP Scopes散播

美國參議院調查發現，2012年至2015年，美國和歐洲的25個醫院/診所報告了250個與內視鏡相關的CRE感染

Promed-mail, Apr. 16, 2016

Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Toleman

Summary

Background Not all patients infected with NDM-1-positive bacteria have a history of hospital admission in India, and extended-spectrum β-lactamases are known to be circulating in the Indian community. We therefore measured the prevalence of the NDM-1 gene in drinking water and seepage samples in New Delhi.

Methods Swabs absorbing about 100 µL of seepage water (ie, water pools in streets or rivulets) and 15 mL samples of public tap water were collected from sites within a 12 km radius of central New Delhi, with each site photographed and documented. Samples were transported to the UK and tested for the presence of the NDM-1 gene, bla_{NDM-1}, by PCR and DNA probing. As a control group, 100 µL sewage effluent samples were taken from the Cardiff Wastewater Treatment Works, Tremorfa, Wales. Bacteria from all samples were recovered and examined for bla_{NDM-1} by PCR and sequencing. We identified NDM-1-positive isolates, undertook susceptibility testing, and, where appropriate, typed the isolates. We undertook Inc typing on bla_{NDM-1}-positive plasmids. Transconjugants were created to assess plasmid transfer frequency and its relation to temperature.

Findings From Sept 26 to Oct 10, 2010, 171 seepage samples and 50 tap water samples from New Delhi and 70 sewage effluent samples from Cardiff Wastewater Treatment Works were collected. We detected bla_{NDM-1} in two of 50 drinking-water samples and 51 of 171 seepage samples from New Delhi; the gene was not found in any sample from Cardiff. Bacteria with bla_{NDM-1} were grown from 12 of 171 seepage samples and two of 50 water samples, and included 11 species in which NDM-1 has not previously been reported, including *Shigella boydii* and *Vibrio cholerae*. Carriage by enterobacteria, aeromonads, and *V cholera* was stable, generally transmissible, and associated with resistance patterns typical for NDM-1; carriage by non-fermenters was unstable in many cases and not associated with typical resistance. 20 strains of bacteria were found in the samples, 12 of which carried bla_{NDM-1} on plasmids, which ranged in size from 140 to 400 kb. Isolates of *Aeromonas caviae* and *V cholerae* carried bla_{NDM-1} on chromosomes. Conjugative transfer was more common at 30°C than at 25°C or 37°C.

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- 印度新德里市自來水和污水中普遍存在NDM-1
- 2/50份水樣本和12/170份污水樣本: 20種不同的細菌種類
(也可在加拿大地表水和污水中找到)

Walsh, Lancet Infect Dis 2011

Combating the spread of carbapenemases in *Enterobacteriaceae*: a battle that infection prevention should not lose

P. Savard
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TABLE I. Infection prevention and antimicrobial stewardship recommendations published to prevent the spread of carbapenem-resistant *Enterobacteriaceae*

Required infection prevention measures
Implement a surveillance programme to identify potential carriers (screening)
Use contact isolation precautions for colonized and infected patients
Cohort colonized and infected patients
Enhance hand hygiene and support with audits
Increase the frequency of environmental cleaning
Limit the use of devices and remove unnecessary devices
Implement antimicrobial stewardship, including a programme
Educate healthcare workers about critical prevention measures
Suggested enhanced infection prevention measures
Limit patient transfers
One-to-one nursing
Decolonize patients with chlorhexidine gluconate baths

Clin Microbiol Infect 2014; 20: 854–861

Thank you for your attention!