CRE
診斷、治療與醫院感染管制

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課程大綱

1. CRE introduction
2. Risk Factors
3. Transmission
4. Clinical Disease
5. Diagnosis
6. Treatment
7. Infection Control of CRE

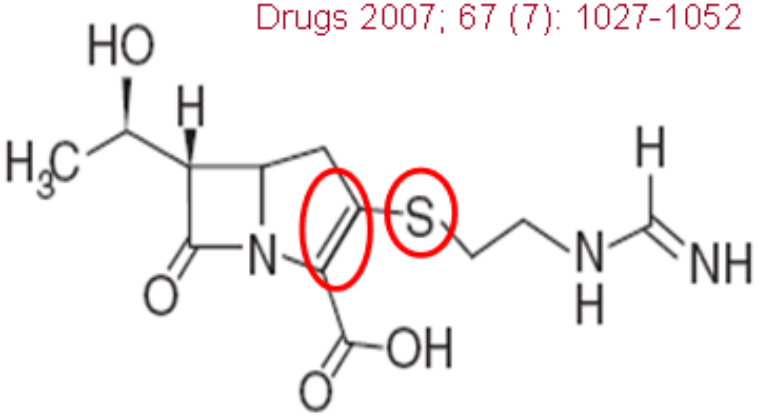
1. CRE簡介

Carbapenem-resistant Enterobacteriaceae (CRE)

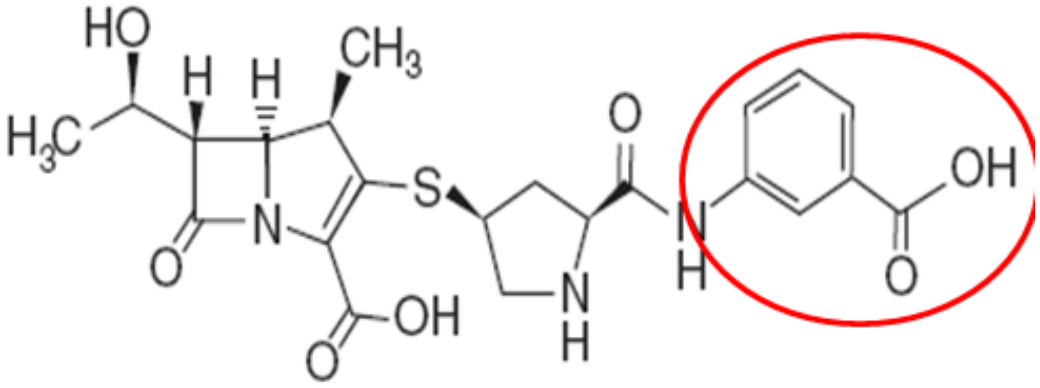
- Carbapenem
  - A broad-spectrum β-lactam antibiotic, the last resort for treatment of serious Gram-negative infections.
- The broadest spectrum
  - Gram(+) and Gram(-) active aerobes and anaerobes, stable to almost all β-lactamases.
- Carbapenemases
  - *Klebsiella pneumoniae* carbapenemase (KPC)
  - New Delhi metallo-β-lactamase (NDM-1)

Carbapenems

Drugs 2007; 67 (7): 1027-1052



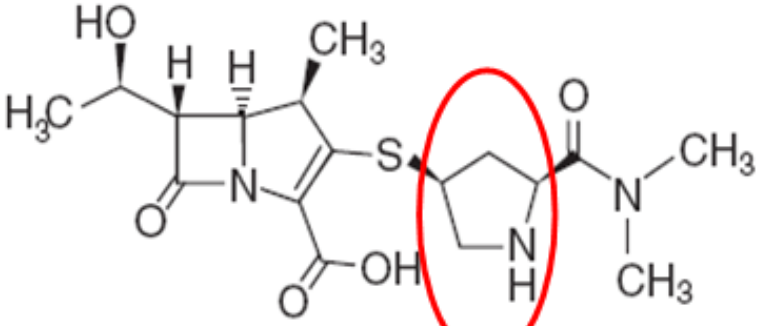
Imipenem



MW ↑,lipophilicity ↑,T1/2 ↑,PB ↑

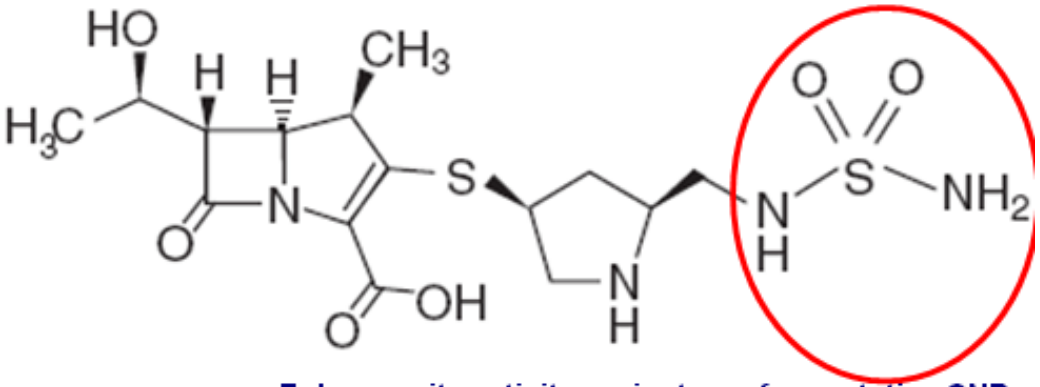
Ertapenem

1987



Superior activity against G(-)

Meropenem



Enhances its activity against non-fermentative GNB

Doripenem

Extended Infusion for Optimizing Dosing of Carbapenems

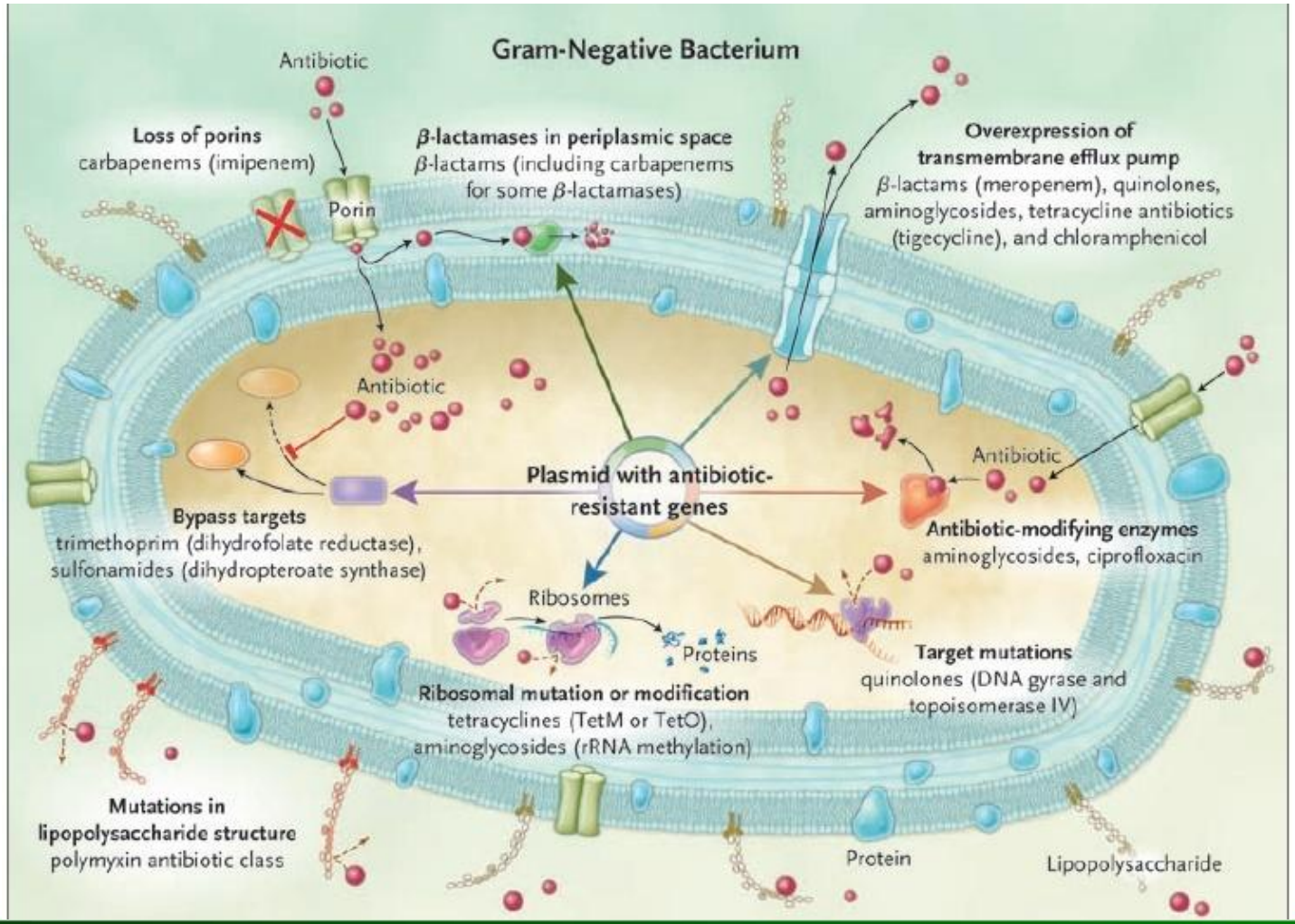
TMUH Antibiotic Dosing Strategy

藥劑部&感控室 2013.06 修訂

Drug	Patient renal function (ClCr)				
	≧ 30 ml/min		< 30 ml/min	Hemodialysis and CAPD	CRRT
Piperacillin/Tazobactam	4.5g q8h, drip 4hr with pump		2.25g q6h, drip 3hr with pump	2.25g q8h, not prolong drip	4.5g q8h, drip 4hr with pump
Ertapenem (Invanz®)	1g qd, drip 4hr with pump		500mg qd, drip 4hr with pump	500mg qd, drip 4hr with pump	
	≧50 ml/min	10~50 ml/min	< 10 ml/min	HD or CAPD	CRRT
Imipenem (Tienam®)	500mg q6h, drip 2hr with pump	250mg q6h, drip 2hr with pump	250mg q12h, drip 2hr with pump	250mg q12h, drip 2hr with pump	250mg q6h, drip 2hr with pump
Meropenem (Mepem®)	1g q8h, drip 3hr with pump	1g q12h, drip 3hr with pump	500mg qd, drip 3hr with pump	500mg qd, drip 3hr with pump (after H/D)	1g q12h, drip 3hr with pump
	≧50 ml/min	30~50 ml/min	10~30 ml/min		
Doripenem (Finibax®)	500mg q8h, drip 4hr with pump	250mg q8h, drip 4hr with pump	250mg q12h, drip 4hr with pump		

資料來源：臺北醫學大學附設醫院藥劑部

Mechanisms of Resistance in Gram-Negative Bacteria and the Antibiotics Affected



資料來源：N Engl J Med 2010; 362: 1804-13

Public Health Threat

HAZARD LEVEL
URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

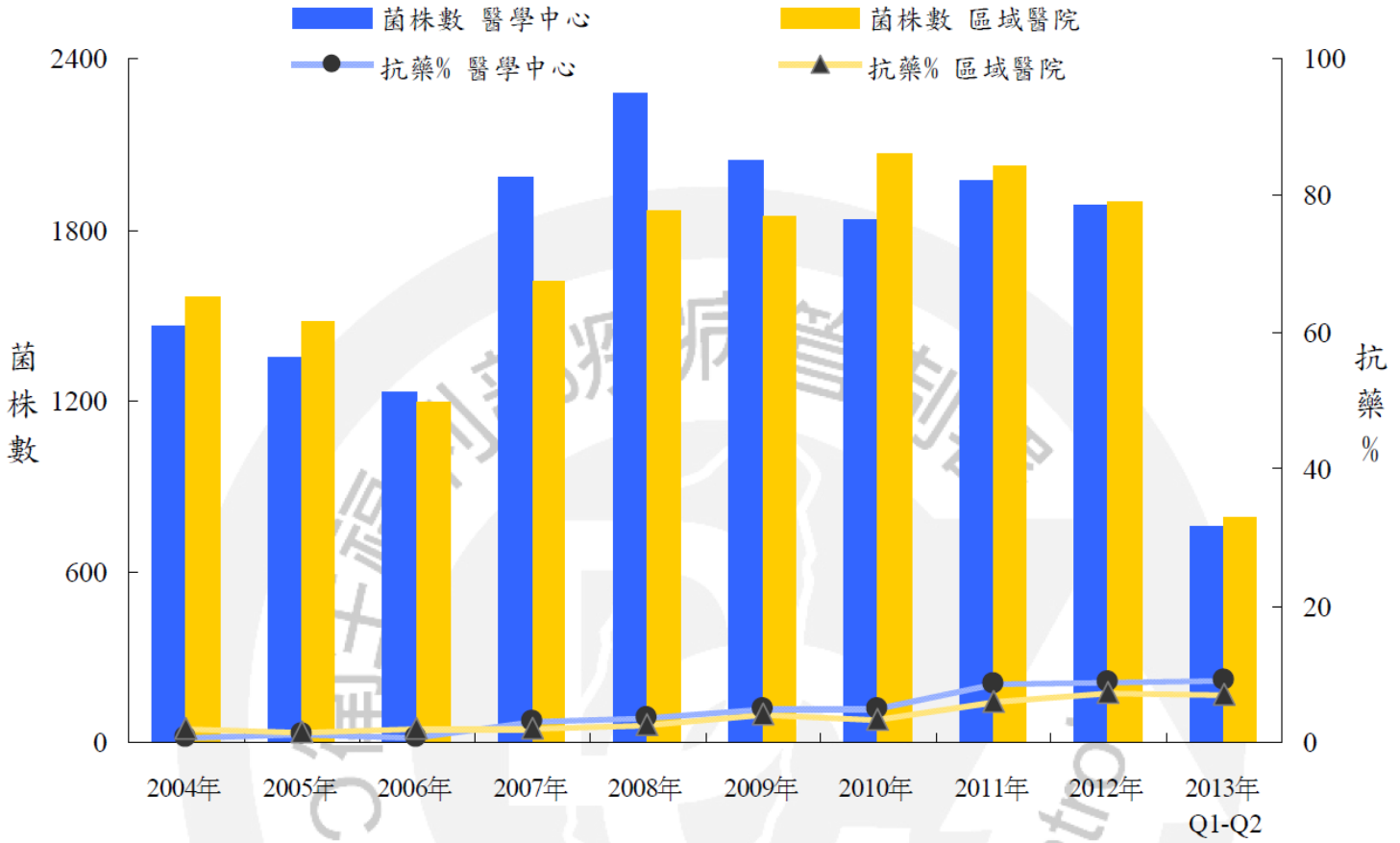
Clostridium difficile (C. difficile), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

- Half of all bloodstream infections caused by CRE result in death.
- At least one type of CRE in healthcare facilities in 44 states in USA.

	Percentage of Enterobacteriaceae healthcare-associated infections resistant to carbapenems	Estimated number of infections	Estimated number of deaths attributed
Carbapenem-Resistant *Klebsiella* spp.	11%	7,900	520
Carbapenem-resistant *E. coli*	2%	1,400	90

資料來源：Antibiotic resistant threats in the United States, 2013, CDC, US

TNIS醫學中心及區域醫院CRE百分比年趨勢圖



腸道菌(Enterobacteriaceae)包含TNIS通報*Enterobacter*、*Escherichia*、*Citrobacter*、 *Serratia*、*Proteus*、*Providencia*、*Klebsiella*、*Morganella*、*Salmonella*、*Shigella*、*Yersinia*等屬 。

資料來源：CDC Taiwan

Factors of Antibiotic Resistance

- Aging population
- Chronic disease patients
- Invasive medical treatments
- Overuse of antimicrobial

The trends are clear and ominous.
No action today means no cure tomorrow.

資料來源：WHO's statement on this World Health Day, April 7, 2011

Carbapenemases(1/2)

- Carbapenem-hydrolyzing β-lactamases
  - Confer resistance to a broad spectrum of β-lactam substrates.
- Ambler molecular classification system
  - Class A, C, and D β-lactamases: a serine residue in the active site.
  - Class B enzymes: zinc for activity. (metallo-β-lactamases)

Carbapenemases(2/2)

Carbapenem β-lactamases

β-Lactamase	Organisms
Class A: KPC 1 to 4	*Klebsiella*, *Escherichia coli*, *Enterobacter*, *Salmonella*, *Pseudomonas*
Class B: metallo-β-lactamases	*Pseudomonas*, *Acinetobacter*, *Enterobacter*, *E. coli*, *Shigella*, *Serratia*
Class C: AmpC-like	*Klebsiella*, *E. coli*, *Enterobacter*, *Pseudomonas*, *Acinetobacter*
Class D: oxacillinases	*Pseudomonas*, *Acinetobacter*, *Enterobacter*, *Serratia*

KPC, *Klebsiella pneumoniae* carbapenemase.

資料來源：Critical Care 2008, 12 (Suppl 4): S5 (doi: 10. 1186/cc6821)

Class A β-lactamases

- Hydrolytic mechanisms that require an active-site serine at position 70.
- Chromosomally-encoded enzymes
- Plasmid-encoded enzymes
  - KPC (*Klebsiella pneumoniae* carbapenemase)

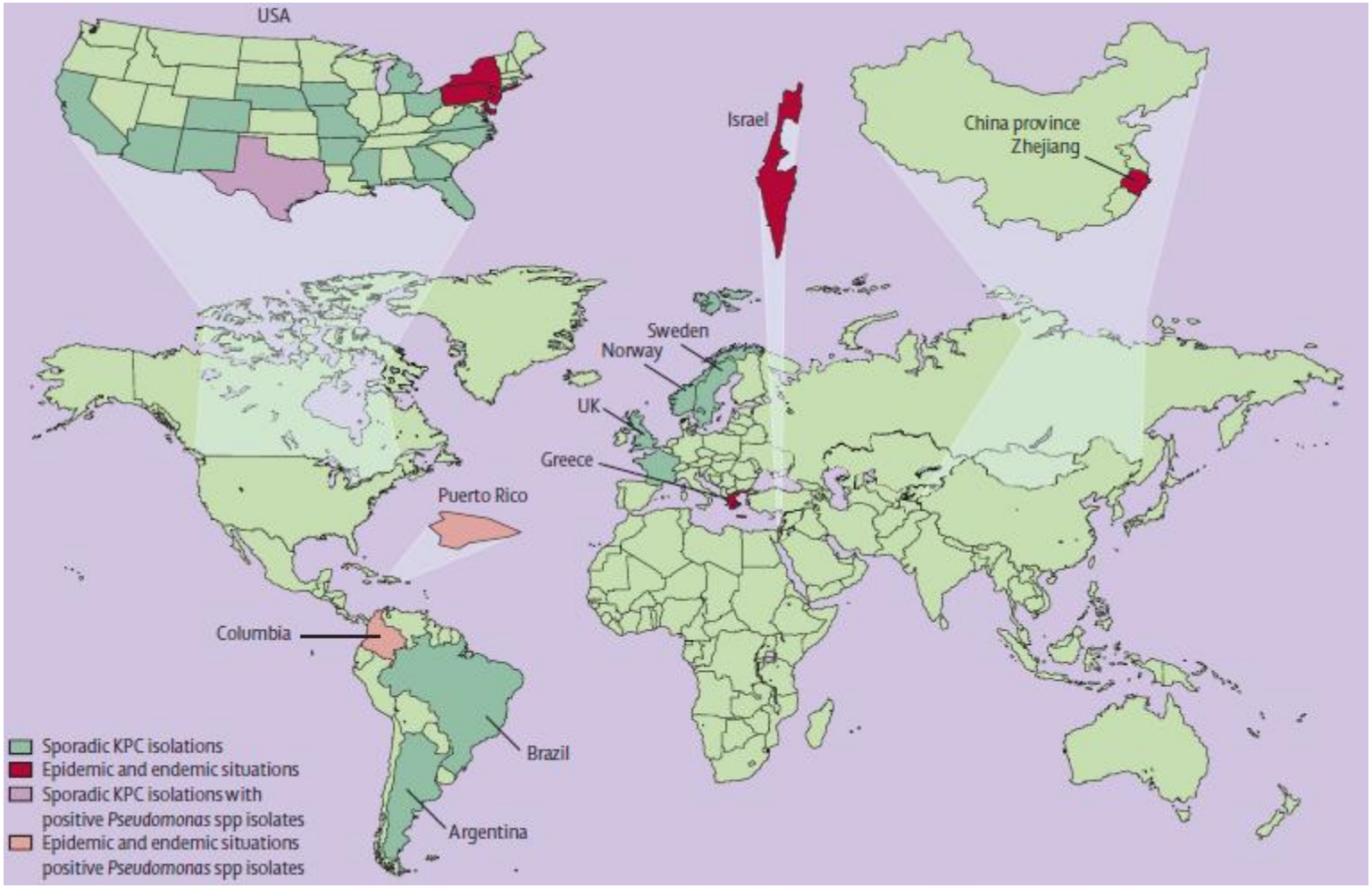
Klebsiella pneumoniae Carbapenemases (KPC) (1/2)

- First described in a clinical isolate of *K. pneumoniae* in the late 1990s in North Carolina.
- Transmissible plasmids and confer resistance to all β-lactams.
- Different variants of KPC enzymes.
- Transmitted from *Klebsiella* to other genera. (*E. coli, Pseudomonas aeruginosa, Citrobacter, Salmonella, Serratia,* and *Enterobacter* spp.)

Klebsiella pneumoniae Carbapenemases (KPC) (2/2)

- Most common carbapenemase in the United States.
- Hospital outbreaks.
- CDC: carbapenem-resistant *Klebsiella* increased from 2 to 10 percent.
- Incidence: higher in long-term acute care facilities than in acute care hospitals.
- Increasingly recovered from other regions of the world, including Europe, Asia, and South America.

Geographic Distribution of KPC Worldwide



資料來源：Lancet Infect Dis 2009; 9: 228-36

International Dissemination of KPC-producing Enterobacteriaceae

資料來源：HEALTHCARE EPIDEMIOLOGY. CID 2011: 53 (1 July). 61

Class B β-lactamases

- Metallo-β-lactamases (MBLs)
  - Dependence upon zinc for efficient hydrolysis of β-lactams.
    - Inhibited by EDTA (an ion chelator), not by β-lactamase inhibitors such as tazobactam, clavulanate, and sulbactam.
- IMP-1:1991 in Japan.
  IMP (19 IMP variants within IMP group)
- VIM, GIM, SPM, and SIM.

Metallo-β-lactamases (MBLs) (1/2)

- Naturally occurring MBLs
  - Chromosomally encoded in *Aeromonas hydrophilia*, *Chryseobacterium* spp., and *Stenotrophomonas maltophilia*.
- Acquired MBLs
  - Genes encoded on integrons residing on large plasmids that are transferable between both species and genera.

Metallo-β-lactamases (MBLs) (2/2)

- In a hospital outbreak involving 62 patients (including 40 intensive care unit patients), for example, an MBL gene (bla_{IMP-4}) spread among seven different Gram-negative genera. (*Serratia, Klebsiella, Pseudomonas, Escherichia, Acinetobacter, Citrobacter,* and *Enterobacter*)

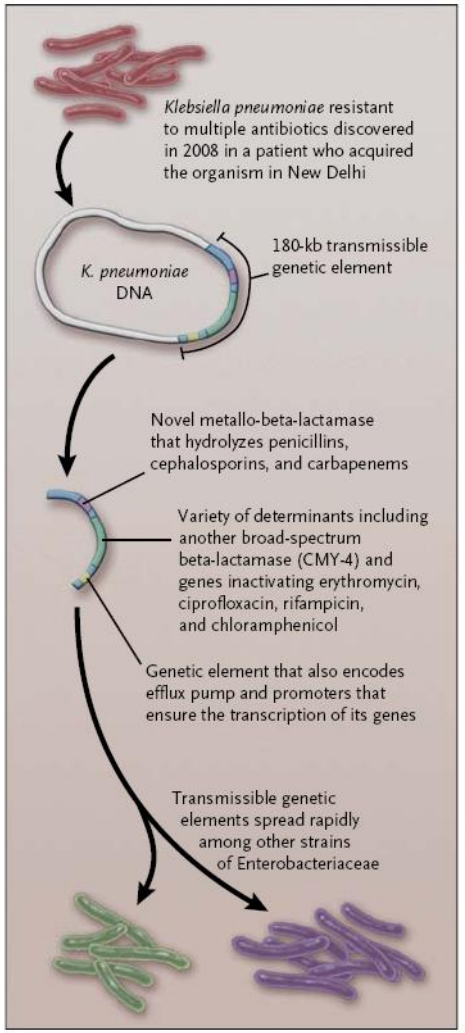
資料來源：Uptodate, Clin Infect Dis. 2005; 41 (11): 1549. and Infect Control Hosp Epidemiol. 2007; 28 (1): 98

New Delhi Metallo-β-lactamase (NDM-1) (1/6)

- NDM-1
  - First described in 2009 in a Swedish patient hospitalized in India with an infection due to *Klebsiella pneumoniae*.
- A mobile genetic element.
- An important emerging resistance trait susceptible to colistin or tigecycline.
- Identified in other Enterobacteriaceae (including *E. coli* and *Enterobacter cloacae*) and non-Enterobacteriaceae.

New Delhi Metallo-β-lactamase (NDM-1) (2/6)

- The Origin and spread of NDM-1
  - Transconjugation
    - Transfer of genetic material between bacteria via cell-to-cell contact.
  - Genetic element
    - Plasmid



資料來源：NEJM 365; 25: 2379

New Delhi Metallo-β-lactamase (NDM-1) (3/6)

- Medical tourism
  - Patients who have traveled and undergone procedures in India and Pakistan, as well as cases reported in Asia, Europe, North America, and Australia.

二〇一〇年八月二十二日 星期日 農曆庚寅年七月十三日 蘋果日報

歐洲至少6死

超級細菌 全球敲警鐘

NDM-1幾打敗所有抗生素 就診宣告知旅遊史

稱為NDM-1（新德里金屬β-內醯胺酶1型）的超級細菌（superbug）已在至少14個國家地區傳出病例，多數集中在印度、巴基斯坦等南亞國家和不少人到南亞動整形手術的英國。目前國內還沒發現，因此專家建議民眾不必刻意提防，但若到過印、巴等國，回國後有發燒等類似感染症狀，應積極就醫。

印巴國院內感染

WHO建議各國準備實施醫院感染控制措施，以限制多重抗藥性病株傳播，並加

台灣未發現病例

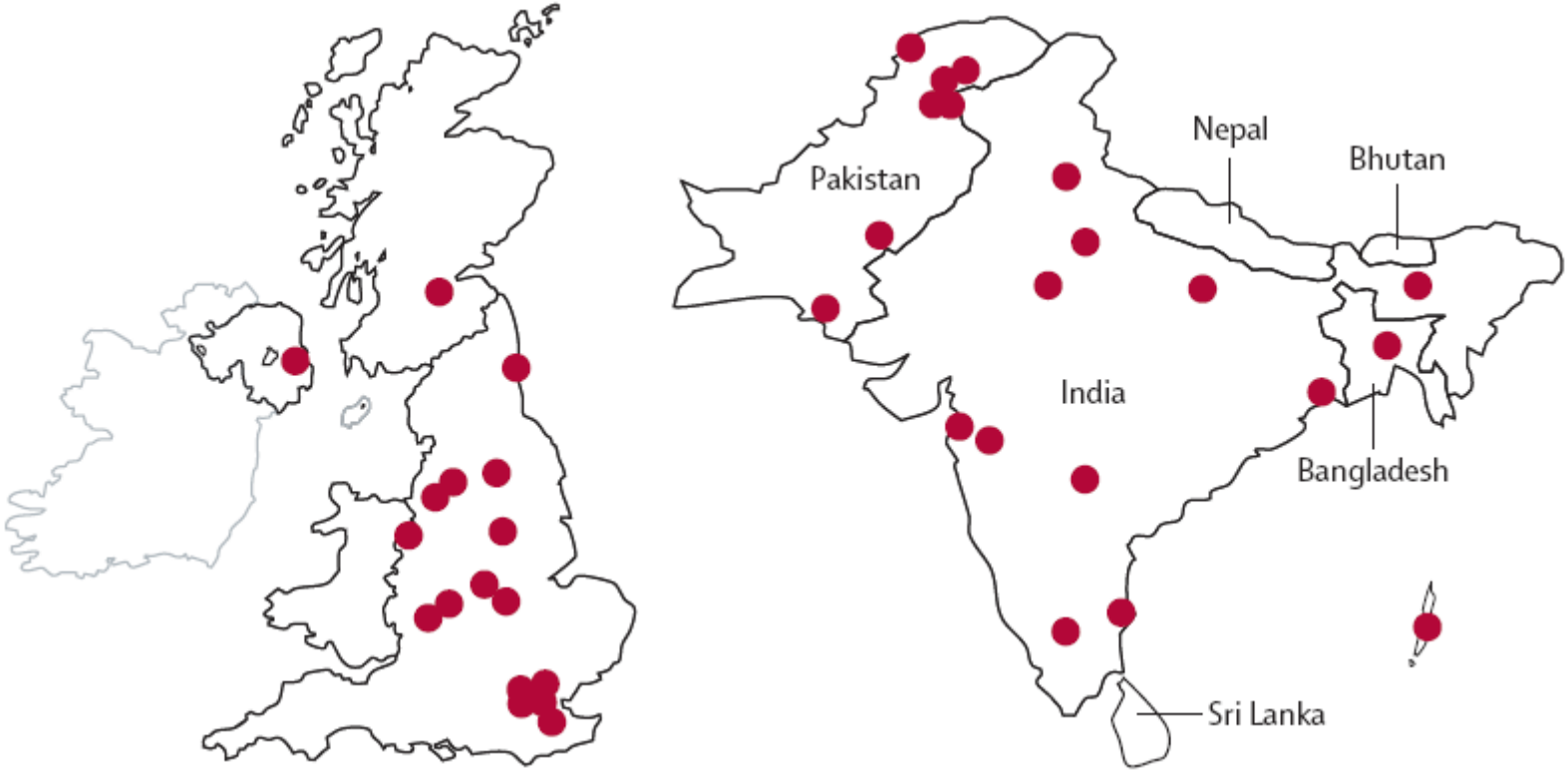
台大醫院小兒感染科主任黃立民說，WHO提醒各國注意，應該是強調兩件事，第一是要各國監視地區內有無出現此細菌，第二是當醫院發現此細菌後，「要能找

黃玉成說，台灣還沒發現超級細菌，民眾不必刻意提防，但若到過曾出現此菌的國家，回台後有類似感染症狀應就醫，並告訴醫師自己的旅遊史，好讓醫師更快速採取有效治療。

資料來源：臺灣蘋果日報

New Delhi Metallo-β-lactamase (NDM-1) (4/6)

- Distribution of NDM-1 Enterobacteriaceae strains in India, Pakistan, Bangladesh, and the UK.



資料來源：Lancet Infect Dis 2010; 10: 597-602

New Delhi Metallo-β-lactamase (NDM-1) (5/6)

- International Dissemination of NDM-1

資料來源：CID 2011: 53 (1 July)

New Delhi Metallo-β-lactamase (NDM-1) (6/6)

- The widespread nonprescription use of antibiotics in India leads to huge selection pressure.

- India also provides cosmetic surgery for other Europeans and Americans, and *bla*$_{\text{NDM-1}}$ will likely spread worldwide.

資料來源：Lancet Infect Dis 2010; 10: 597-602

What's Special about This New Type of Resistance Labelled as NDM-1?

- New resistance pattern has been reported in many different types of bacteria.
- There is no significant new drug development for antimicrobials.
- The resistance pattern is governed by a set of genes that can move easily from one bacterium to another.
- It has been found in the most commonly encountered bacterium in the human population, *E. coli*.

資料來源：World Health Organization

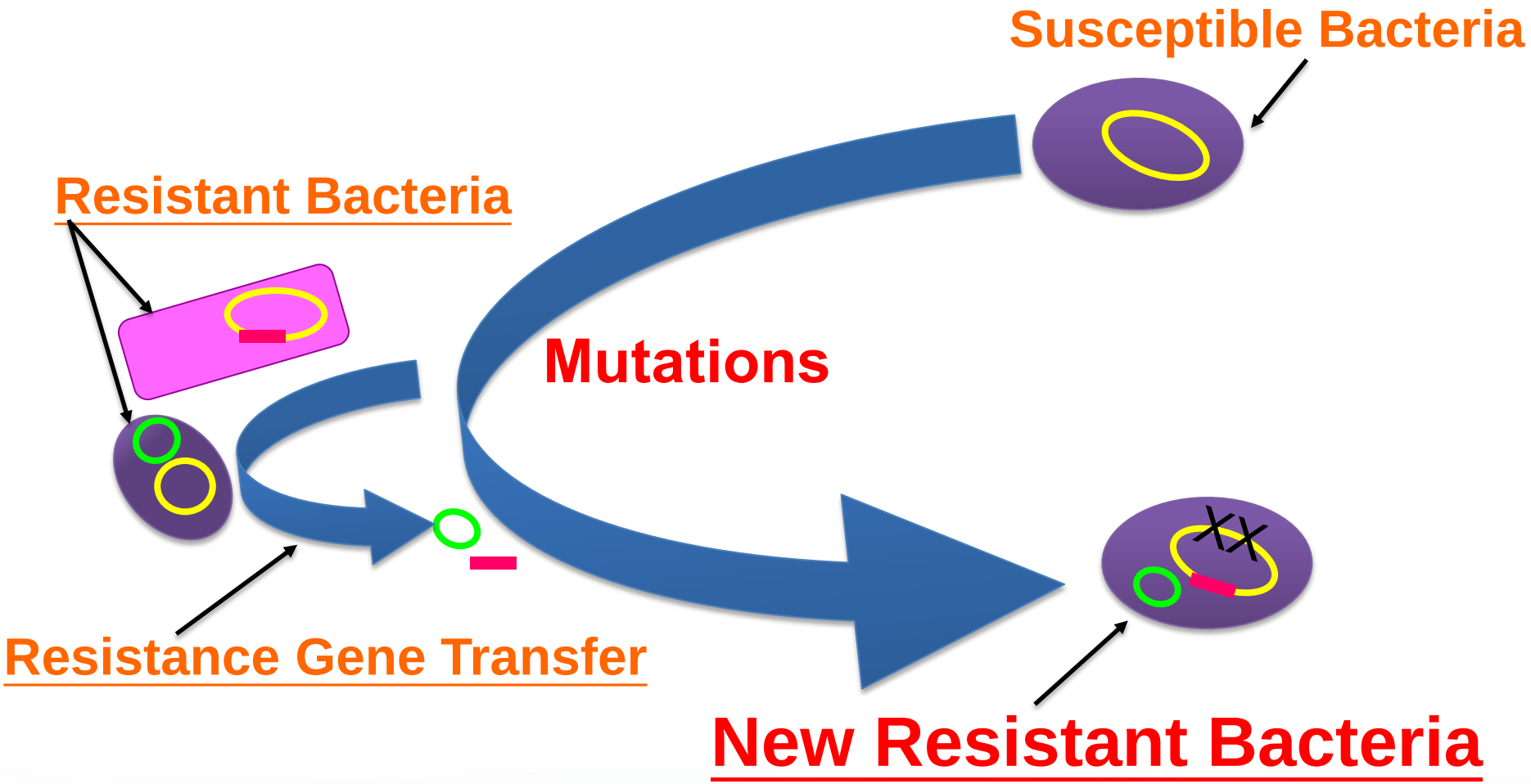
2. Risk Factors

Risk Factors

- Carbapenemase-producing organisms can arise from previously carbapenemase-negative strains by acquisition of genes from other bacteria.

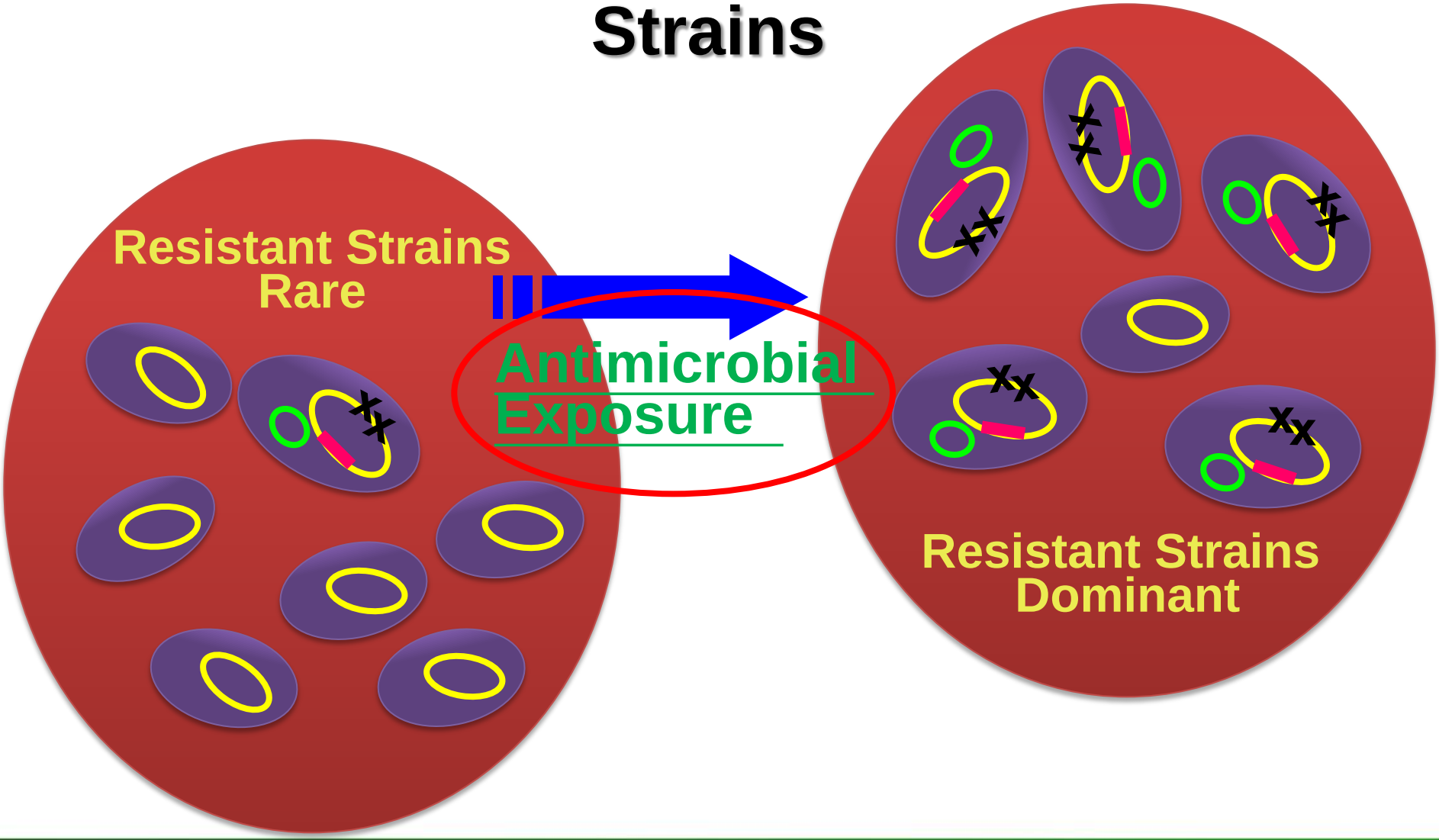
- Use of broad spectrum cephalosporins and/or carbapenems.

Emergence of Antimicrobial Resistance



資料來源：CDC USA

Selection for Antimicrobial-resistant Strains

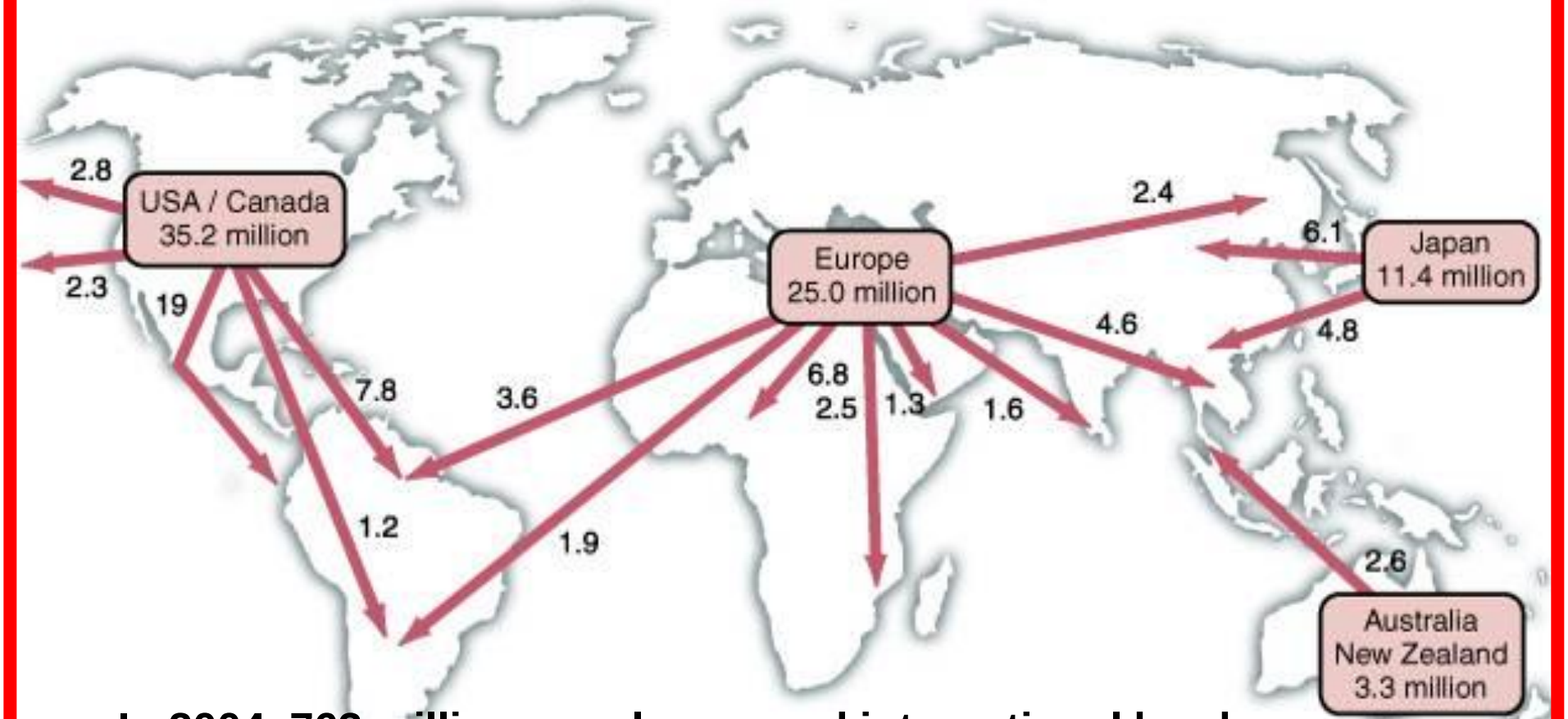


資料來源：CDC USA

Additional Risk Factors

- Trauma
- Diabetes
- Malignancy
- Organ transplantation
- Mechanical ventilation
- Indwelling urinary or venous catheters
- Overall poor functional status or severe illness
- Received medical care in India and Pakistan
  - NDM-1-producing Enterobacteriaceae.

Increasing International Travel



In 2004, 763 million people crossed international borders, reflecting an increase of 73 percent over the course of 15 years.

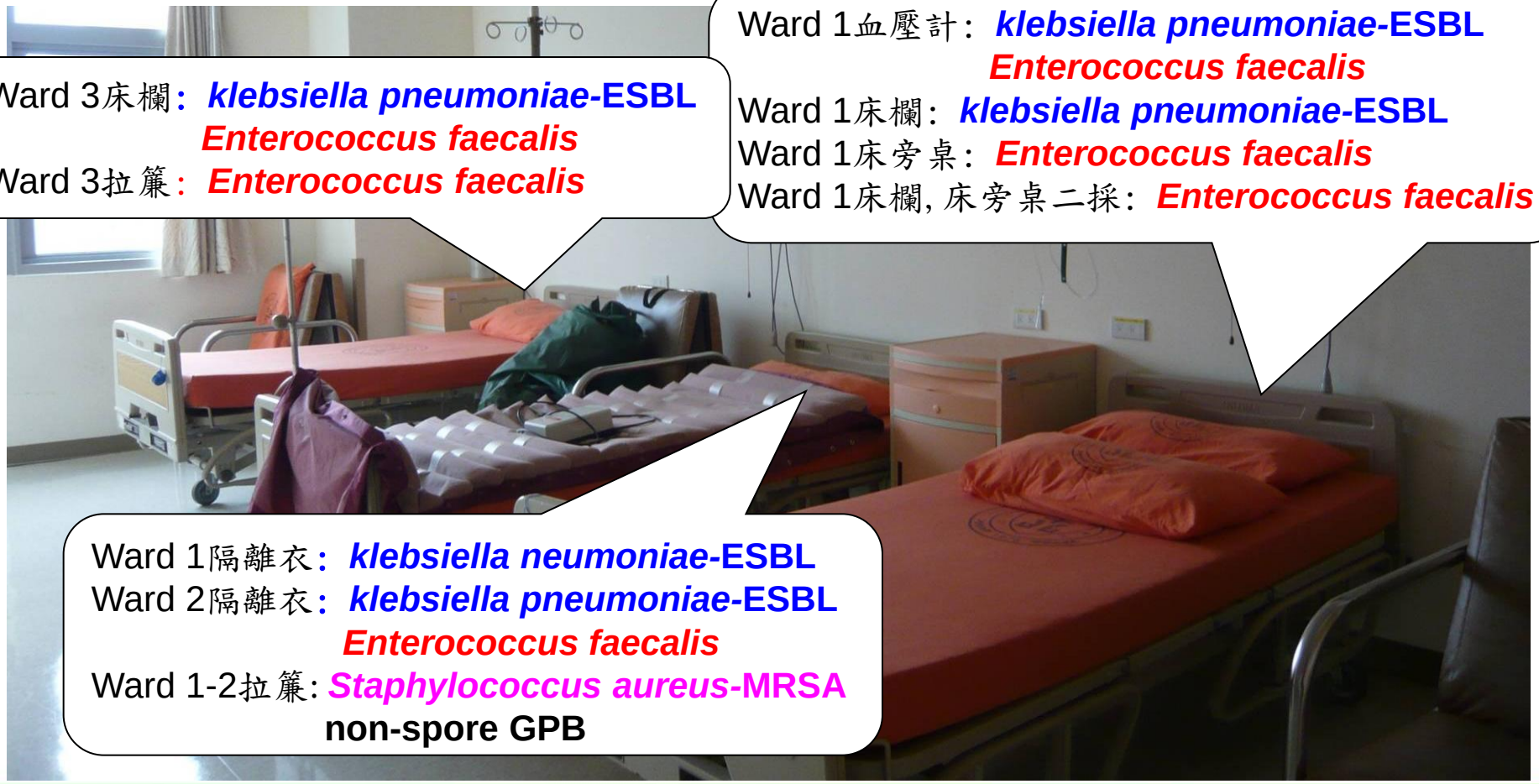
資料來源：N Engl J Med 354 2 January 12, 2006

3. Transmission

Transmission

- Transposons or plasmids
  - On mobile genetic elements, and have the potential for widespread transmission to other isolates and genera of bacteria.
- Enterobacteriaceae, which may harbor carbapenemase-encoding genes, can spread from person to person.
- Cross-infection within and outside of healthcare systems.

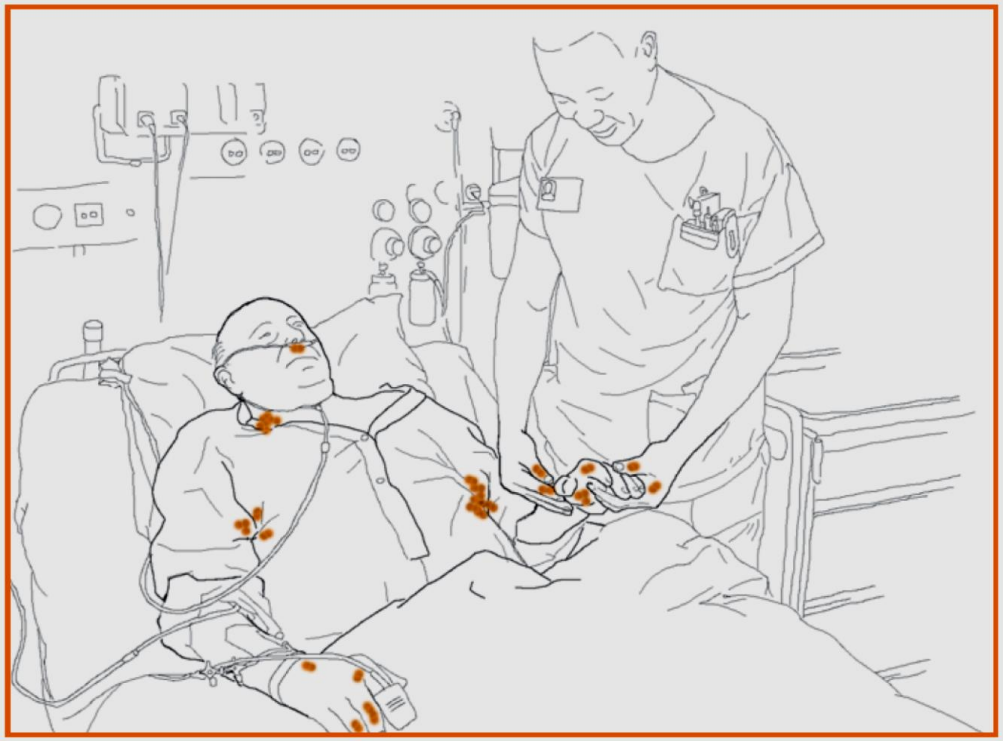
Cross-infection Inside the Hospital



資料來源：臺北醫學大學附設醫院感染管制室

Organisms Transfer from Patient to HCW's Hand

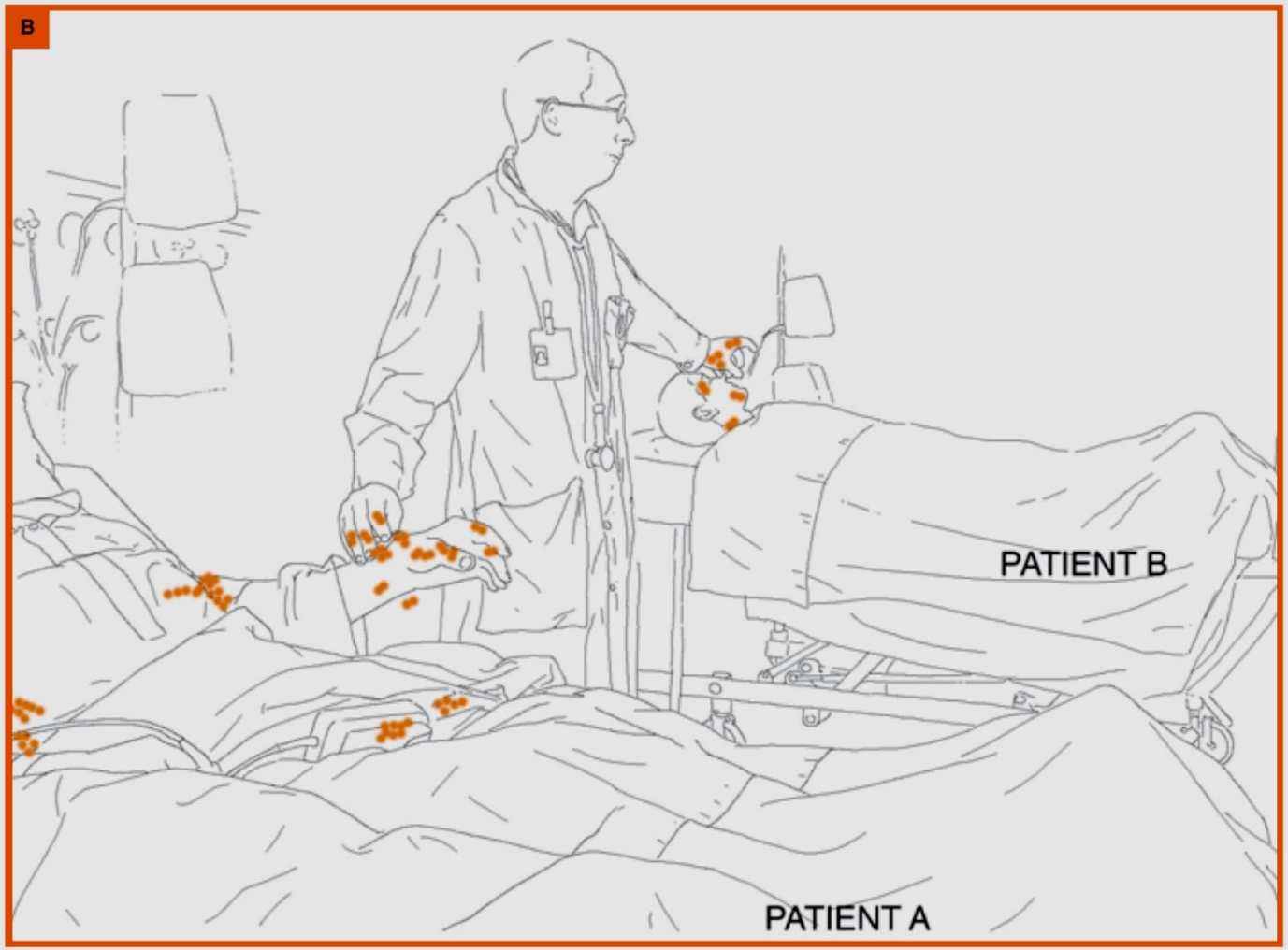
Figure I.7.2
Organism transfer from patient to HCWs' hands



Contact between the HCW and the patient results in cross-transmission of microorganisms. In this case, Gram-positive cocci from the patient's own flora transfer to HCW's hands. Reprinted from Pittet, 2006[885] with permission from Elsevier.

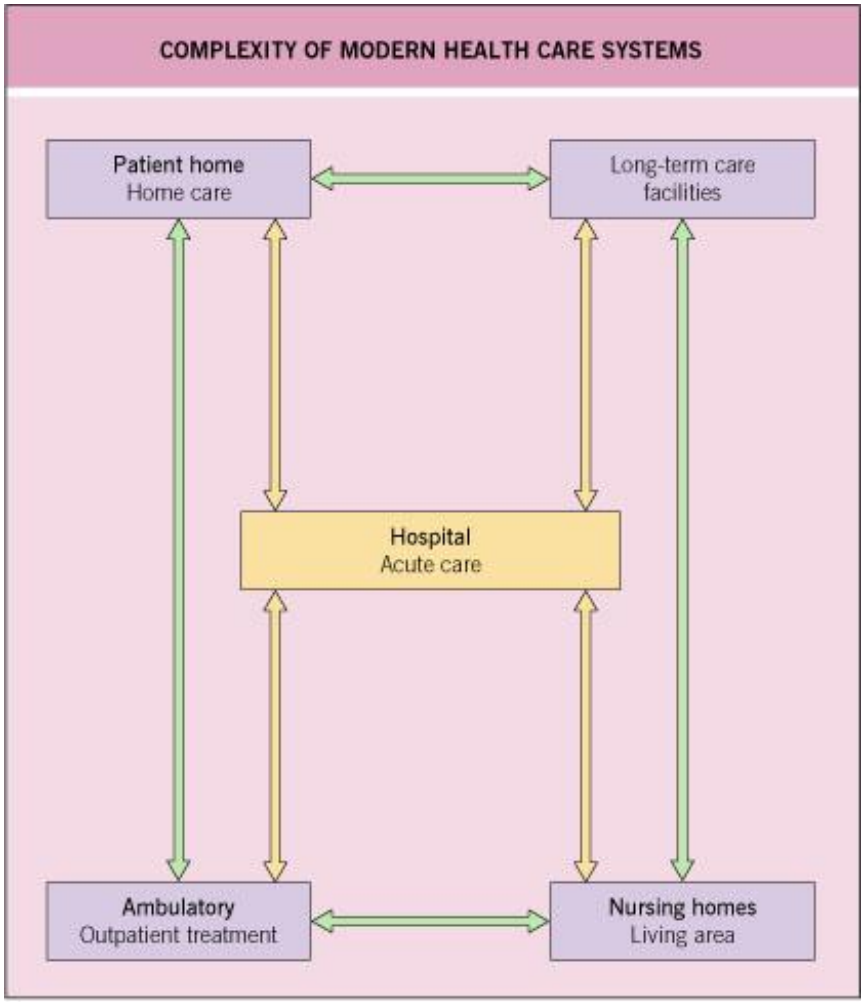
資料來源：WHO

Failure to Cleanse Hands Results in between Patient Cross-transmission



資料來源：WHO

Modern Healthcare Systems



資料來源：Elsevier 2004. Infectious Diseases 2e

Transmission

- Public water supplies
  - NDM-1-positive bacteria in India, the potential for environmental dissemination.

Antibiotic resistance shows up in India's drinking water

Discovery of NDM-1 outside hospital environment raises alarm.

Naomi Lubick

Bacteria carrying a gene that confers resistance to a major class of antibiotics have shown up in samples of drinking water and sewage seepage from New Delhi, researchers report in *The Lancet Infectious Diseases* today[1]. This raises the danger that people will be exposed to disease-causing bacteria that cannot be treated by antibiotics.

Antibiotic resistance genes have been found in bacteria in drinking water and sewage, far the hospitals the usually haunt.

Gurinder Osan / AP Photo

The resistance is bestowed by a gene, bla_{NDM-1}, that encodes the enzyme New Delhi metallo-β-lactamase 1 (NDM-1). These genes can be passed easily between bacteria by discrete rings of DNA called plasmids. The enzyme blocks the activity of a range of antibiotics including the carbapenems — drugs of last resort for resistant infections — which might be used to treat, for example, urinary-tract infections triggered by the bacterium *Escherichia coli* or lung infections resulting from *Klebsiella pneumoniae*. NDM-1-positive strains of both species have previously been found in hospitals in India and Pakistan.

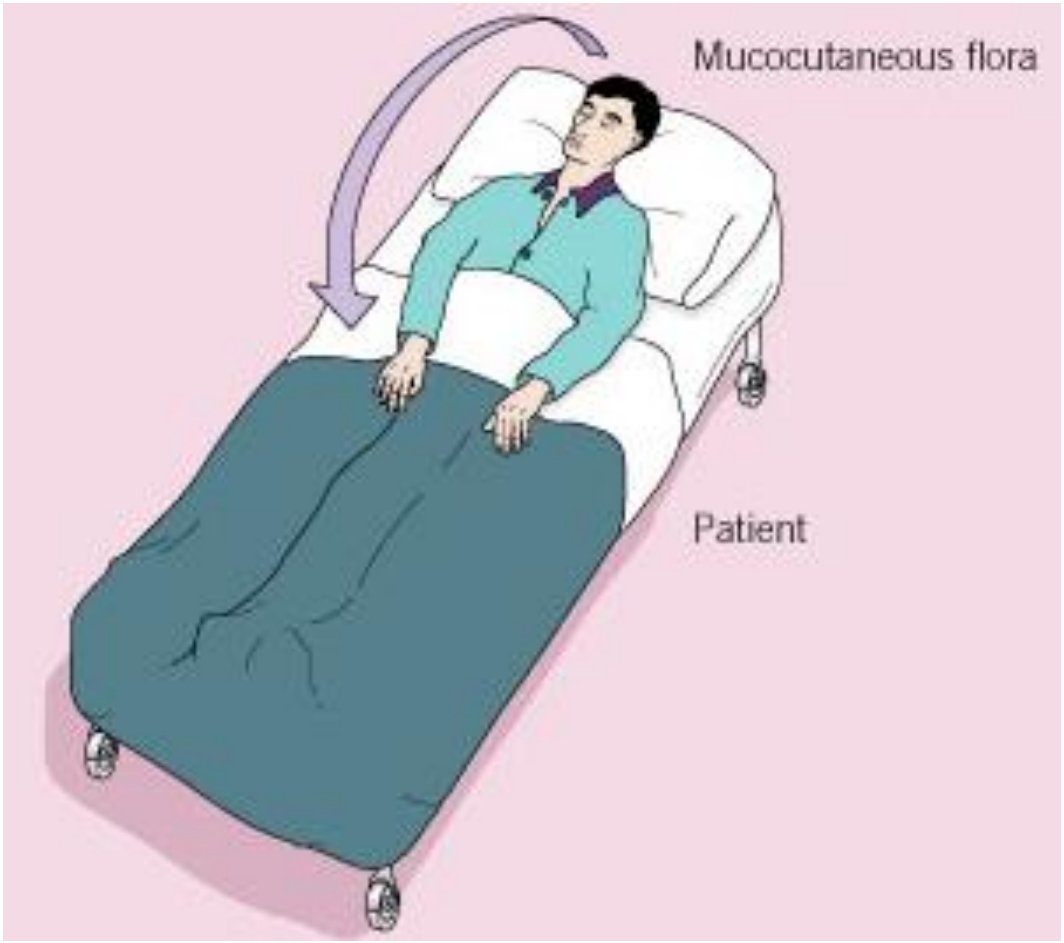
資料來源：Nature 2011 April 7

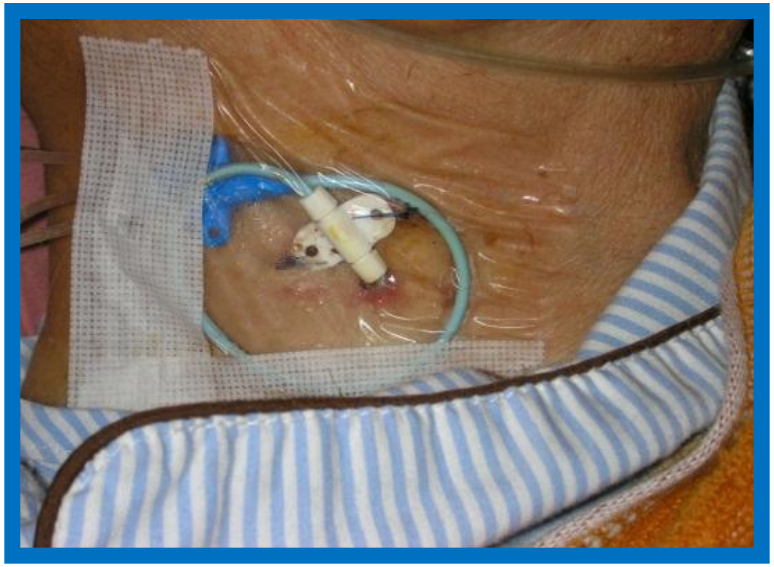
4. Clinical Disease

Clinical Disease

- Clinical infections or asymptomatic colonization.
- Blood stream infections, ventilator-associated pneumonia, urinary tract infection, and central venous catheter infections.
- Isolated from respiratory tract specimens, abdominal swabs, catheters, abscesses, urine, and surgical wounds.
- Sporadic hospital-acquired infections and outbreaks due to hospital-based clonal spread in both tertiary and community hospitals.

Healthcare-associated Infections





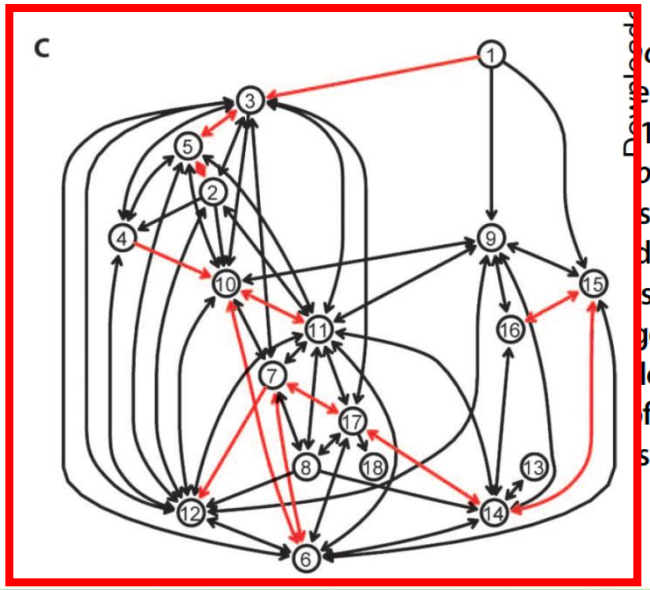
Hospital Outbreak of CRE

RESEARCH ARTICLE

NOSOCOMIAL INFECTION

Tracking a Hospital Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* with Whole-Genome Sequencing

Evan S. Snitkin,[1] Adrian M. Zelazny,[2] Pamela J. Thomas,[1] Frida Stock,[2]
NISC Comparative Sequencing Program,[3] David K. Henderson,[2]
Tara N. Palmore,[2]* Julia A. Segre[1]*



oniae is a major cause of nosocomial infections, primarily among im-
e of strains resistant to carbapenems has left few treatment options,
1, the U.S. National Institutes of Health Clinical Center experienced an
oniae that affected 18 patients, 11 of whom died. Whole-genome se-
solates to gain insight into why the outbreak progressed despite early
dures. Integrated genomic and epidemiological analysis traced the
s from a single patient who was discharged 3 weeks before the next
genomic comparisons provided evidence for unexpected transmission
logical data pointing to possible explanations for these transmissions.
f genomic and epidemiological data can yield actionable insights and
sion.

資料來源：Science Translational Medicine 2012

The First Reported Death…

- In August 2010, a Belgian man who was hospitalised with a major leg injury was involved in a car accident during a trip to Pakistan.
- A doctor involved in his treatment said, “He had already infected before repatriating to Belgium.”
- He died despite being administered colistin, a powerful antibiotic…

First NDM-1 Patient (Colonized) in Taiwan

CASE REPORT

First Identification of a Patient Colonized With *Klebsiella pneumoniae* Carrying bla_{NDM-1} in Taiwan

Hua-Shin Wu[1,4], Te-Li Chen[1,2,4,5], Isaac Chun-Jen Chen[3], Mu-Shun Huang[3], Fu-Der Wang[1,4,5], Chang-Phone Fung[1,4,5], Shou-Dong Lee[4,5]*

[1]Division of Infectious Diseases, [2]Immunology Research Center, and Departments of [3]Emergency Medicine and [4]Medicine, Taipei Veterans General Hospital, and [5]Department of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

New Delhi metallo-β-lactamase 1 (NDM-1) is a novel type of metallo-β-lactamase (MBL). *Enterobacteriaceae* carrying this NDM-1 encoding gene, bla_{NDM-1}, have been identified worldwide. Bacteria carrying bla_{NDM-1} are not only resistant to carbapenem, but also highly resistant to many classes of antibiotics, which indicate the importance of prompt identification of these bacteria and implementation of strict infection control measures to prevent their transmission. Here, we report the first identification and management of a patient colonized with *Klebsiella pneumoniae* carrying bla_{NDM-1} in Taiwan, who returned from New Delhi where he had been hospitalized for a gun-shot injury. [*J Chin Med Assoc* 2010; 73(11):596–598]

Key Words: antibiotics, drug resistance, *Enterobacteriaceae*, New Delhi metallo-β-lactamase 1, Taiwan

資料來源：J Chin Med Assoc 2010; 73 (11): 596-598

First NDM-1 Patient (Infected) in Taiwan

疾病管制局確認首例NDM-1腸道菌感染症確定病例，請前往國外接受醫療處置之民眾提高警覺

資料來源: 公關室 Public Relations Office
日期: 2011/1/14

SHARE

疾病管制局今日確認本(2011)年首例NDM-1腸道菌感染症個案，該名病例為56歲男性，有尿毒症病史，於去(2010)年10月前往中國江西省進行腎臟移植，10月下旬回國，並因下腹部痛前往某醫院就醫，其腹部核磁共振掃描(MRI)，發現腹腔內有積液，於11月5日接受引流，並將引流液送細菌培養分離出Carbapenem抗藥性克雷白氏菌，之後陸續於11月17日引流液、11月27日尿液、12月21日尿液亦培養出相同菌株。經該院抗藥性監視系統針對所分離出Carbapenem 抗藥性克雷白氏菌之抗藥性基因篩檢，高度懷疑該菌株帶有NDM-1基因，而於本年1月10日依法進行通報，由於該院平時對所有Carbapenem腸道菌個案即依照院內感染之相關隔離措施，且個案入院後一直於單人房中接受照護，該院去年10月至12月所檢出之Carbapenem抗藥性腸道菌株，除本個案外，並未發現NDM-1腸道菌，未有證據顯示於院內造成傳播，且本局及國內各大醫學中心和研究機構實驗室所收集之CRE菌株共約1000餘株，皆未曾檢出NDM-1陽性菌株，故該名病例懷疑為境外移入個案，但仍須更多資訊再行研判。

多重抗藥性細菌及其全球散播為全球持續關注的公共衛生議題，WHO並已列為今年四月七日世界衛生日之主題，其所擬訂之四大防治面向包括，一、建立抗藥性通報機制。二、合理使用抗生素及抗生素教育。三、立法管理抗生素使用。四、加強醫療機構感染控制能力。疾病管制局依據WHO該四大面向架構，制定相關防疫政策，如持續加強醫療院所落實手部衛生及標準隔離防護措施；推動國內醫院之抗藥性細菌監測及院感等相關計畫。

NDM-1腸道菌感染症已自去年9月9日公告為第四類法定傳染病(通報定義如附件)，疾病管制局呼籲各醫療機構，病患只要有國外旅遊史，尤其接受手術、侵入性醫療服務或傷口處理等，經檢測為Carbapenem抗藥性腸道菌，且懷疑為NDM-1腸道菌感染症之個案者，應於24小時內完成通報，該局再次提醒各醫療機構應加強NDM-1院內宣導有關通報及感控等相關事宜。

資料來源：CDC Taiwan

Cases of Metallo-β-lactamase Producing Enterobacteriaceae in USA

Table 1. Cases of Metallo-β-Lactamase–Producing *Enterobacteriaceae* in the United States Reported to CDC, 2009–2010

Case	MBL type	Culture date	Organism	Culture site	Received medical care outside United States	Additional patient information
1	NDM	Apr 2009	*Enterobacter cloacae*	Urine	Yes	Hospitalization in India
2	NDM	Dec 2009	*Klebsiella pneumoniae*	Urine	Yes	Hospitalization in India
3	NDM	May 2010	*Escherichia coli*	Urine	No	Travel in India, history of multiple comorbidities, indwelling medical device
4	NDM	Sep 2010	*K. pneumoniae*	Respiratory	Yes	Hospitalization in Pakistan
5	NDM	Sep 2010	*E. coli*	Respiratory	Yes	Received medical care in India, no hospitalizations
6	NDM	Dec 2010	*K. pneumoniae*	Urine	Yes	Hospitalization in India
7	NDM	Feb 2011	*K. pneumoniae*	Respiratory	Yes	Hospitalization in India
8	IMP	Nov 2009	*K. pneumoniae*	Urine	No	No known travel outside United States
9	IMP	May 2010	*K. pneumoniae*	Urine	No	No known travel outside United States
10	IMP	Jun 2010	*K. pneumoniae*	Urine	No	No known travel outside United States
11	VIM	Jul 2010	*K. pneumoniae*	Blood	Yes	Hospitalization in Greece
12	VIM	Sep 2010	*K. pneumoniae*	Urine	Yes	Hospitalization in Italy
13	VIM	Oct 2010	*K. pneumoniae*	JP drain	No	Overlapping ICU stay with case-patient 11 during United States hospitalization

NOTE. MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; IMP, ''active on imipenem''; VIM, Verona integron-encoded metallo-β-lactamase; ICU, intensive care unit.

資料來源：CID 2011: 53 (1 July)

5. 診斷

當醫院出現多重抗藥性（如:CRE）病人，特別是帶有易於擴散性基因（如：KPC或NDM）的CRE病人，如何即刻介入感染管制措施？

MIC Breakpoints for Carbapenems

- Clinical Laboratory and Standards Institute (CLSI) :Enterobacteriaceae with elevated MICs to carbapenems (2–4 μg/mL) or reduced disk diffusion zones be tested for production of a carbapenemase using the modified Hodge test (MHT)

	Previous breakpoints (M100-S19) MIC (μg/mL)			Revised breakpoints (M100-S20) MIC (μg/mL)		
Agent	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Doripenem	…	…	…	≤1	2	≥4
Ertapenem	≤2	4	≥8	≤0.25	0.5	≥1
Imipenem	≤4	8	≥16	≤1	2	≥4
Meropenem	≤4	8	≥16	≤1	2	≥4

資料來源：CID 2011: 53 (1 July)

Clinical Laboratory Testing

- Identification of *E. coli* or *K. pneumoniae* with overt resistance to any of the carbapenems should raise suspicion that it may be harboring a carbapenemase enzyme.

法定傳染病

- 其他傳染病

福氏內格里阿米巴腦膜腦炎	貓抓病	NDM-1腸道菌感染症
發熱伴血小板減少綜合症	細菌性腸胃炎	常見腸道寄生蟲病簡介
中華肝吸蟲感染症	旋毛蟲感染症	肺吸蟲感染症
廣東住血線蟲感染症	鸚鵡熱	亨德拉病毒及立百病毒感染症
第二型豬鏈球菌感染症	病毒性腸胃炎	沙門氏菌感染症
疥瘡	頭蝨感染症	李斯特菌症
隱球菌症	CRE抗藥性檢測	VISA/VRSA抗藥性檢測
肺囊蟲肺炎	淋巴絲蟲病	

CRE 防治指引

(二) 若醫療機構於病患臨床檢體分離出CRE，可經由傳染病通報系統之「其他傳染病」項下「CRE抗藥性檢測」辦理通報及送驗，如下圖。

圖一、通報畫面

圖二、防疫檢驗結果報告單-檢驗結果顯示

三、檢體採集運送方式

6. 治療

Antimicrobial Therapy for CRE(1/3)

- The optimal treatment of infection due to carbapenemase-producing organisms is uncertain.
- Because the presence of a KPC or metalloenzyme carbapenemase confers resistance to all penicillins, cephalosporins, and carbapenems, selection of antibiotic therapy should be tailored to antimicrobial susceptibility results for agents outside the β-lactam and carbapenem classes.

Antimicrobial Therapy for CRE(2/3)

- Combination antimicrobial therapy with two or more agents for patients with severe infections (including bacteremia) due to a carbapenemase-producing Gram-negative organism.

- CRE: High mortality, emergence of resistance during monotherapy, and the lack of clearly effective single drug alternatives.

Antimicrobial Therapy for CRE(3/3)

Table 5. Recommended Definitive Therapy for Serious Infections, Including VAP and Bloodstream Infections, Caused by Drug-Resistant Gram-Negative Bacteria.*

Drug-Resistant Pathogen	Recommended Therapy
Extended-spectrum β-lactamase–producing Enterobacteriaceae ESBL	Meropenem, 1–2 g given intravenously every 8 hr; or imipenem, 500 mg given intravenously every 6 hr; doripenem, 500 mg given intravenously every 8 hr or as a 1-hr or 4-hr infusion
Carbapenemase-producing Enterobacteriaceae	Colistin, 2.5–5.0 mg of colistin base/kg of body weight/day given in 2 to 4 divided doses† (equivalent to 6.67–13.3 mg of colistimethate sodium/kg /day); or tigecycline, 100 mg given intravenously as a loading dose, then 50 mg given intravenously every 12 hr

資料來源：N Engl J Med 2010; 362: 1804-13

Tigecycline(1/2)

- Glycylcycline antibiotic derived from minocycline.

- Gram-positive pathogens (including MRSA, VRE, and penicillin-resistant *Streptococcus pneumoniae*), Gram-negatives (important exceptions include *Pseudomonas* and *Proteus* species), anaerobes, and atypical species.

Tigecycline(2/2)

- Complicated skin and skin-structure infections and complicated intra-abdominal infections.
- Given concerns regarding achieving adequate serum drug concentrations, caution should be used for the treatment of patients with bacteremia.
- Associated with an increased risk of all-cause mortality, most clearly among patients with hospital-acquired pneumonia.

Polymyxins

- Retain activity against most multidrug-resistant Gram-negative pathogens.

- Combining polymyxin B with other antimicrobial agents (e.g., tigecycline, carbapenems or rifampin) can result in enhanced *in vitro* activity.

7. Infection Control of CRE

多重抗藥性菌種院內感染之影響

一、病患

- 延長住院日數，增加經濟負擔。
- 增加身心痛苦、造成殘疾、失去生命。

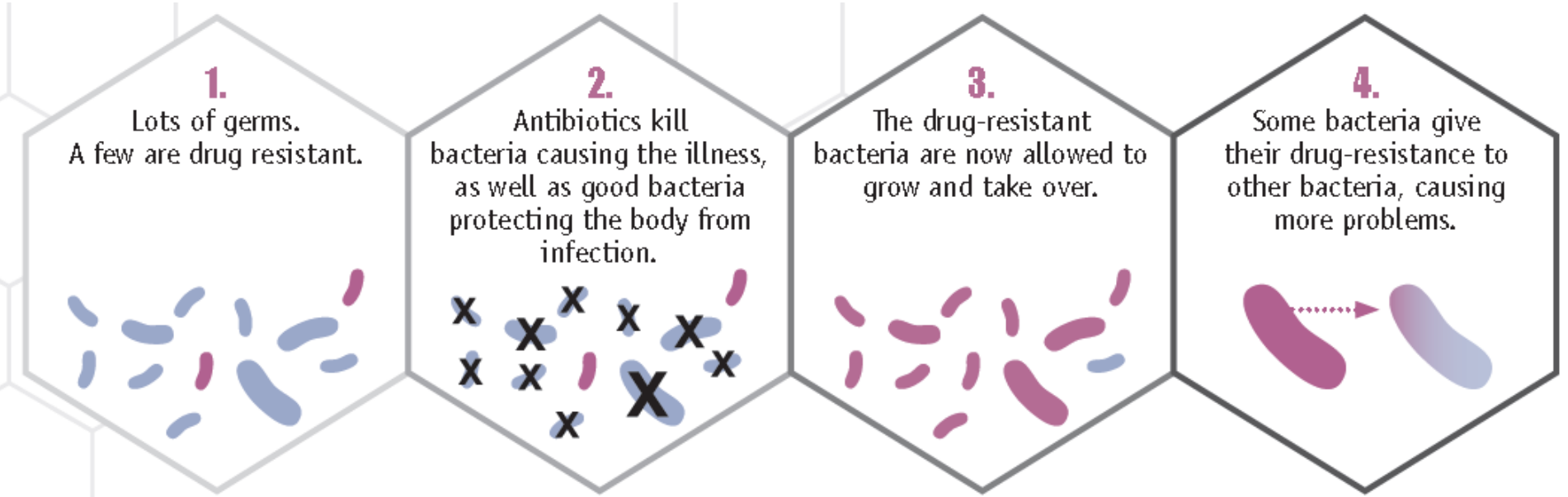
二、工作人員

- 增加工作量，增加感染之危險性。

三、醫院

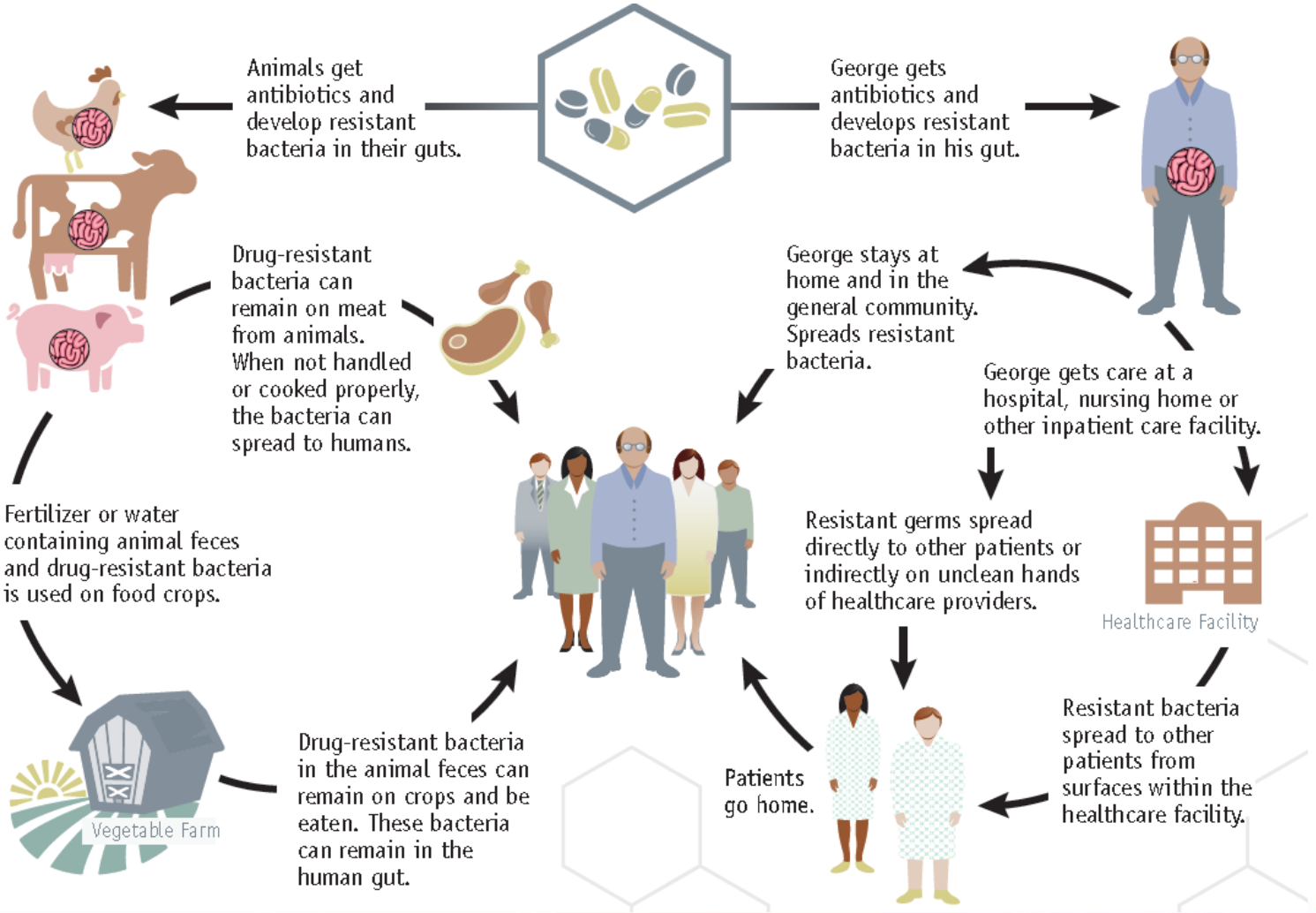
- 關閉病房、院譽受損、負法律責任。

How Antibiotic Resistance Happens



資料來源：Antibiotic resistant threats in the United States, 2013, CDC, US

How Antibiotic Resistance Spreads



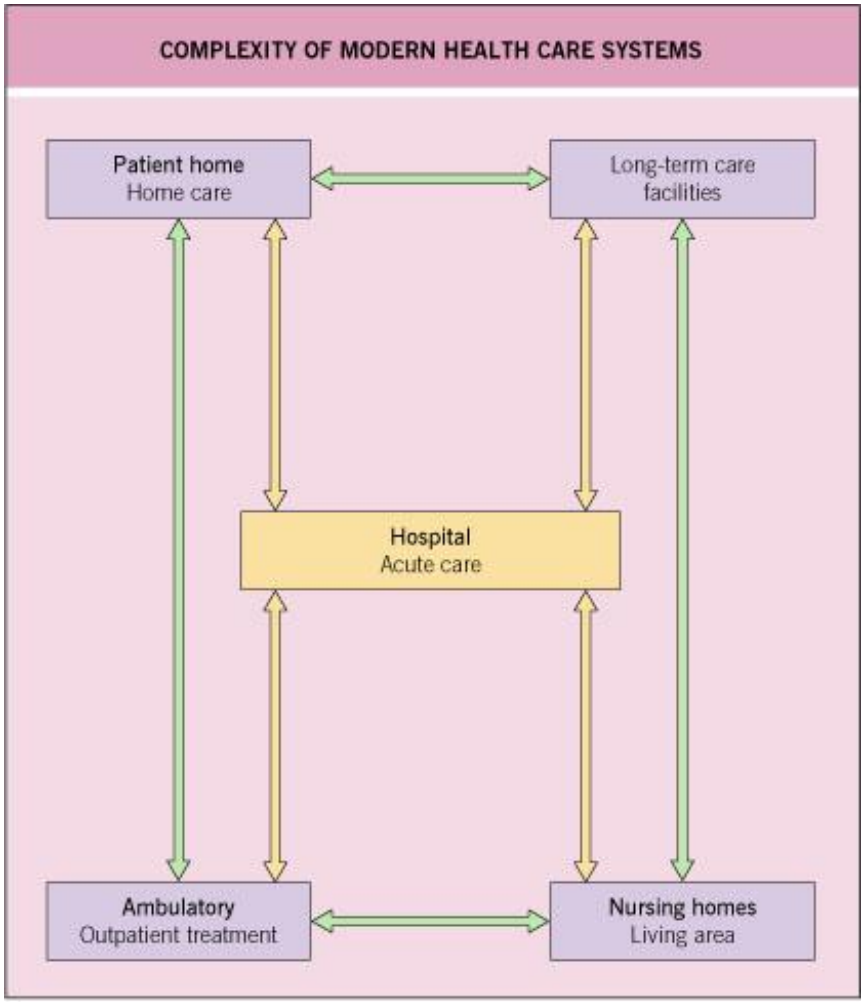
資料來源：Antibiotic resistant threats in the United States, 2013, CDC, US

The Strategy Encompasses Actions

- Surveillance for antimicrobial resistance, education of healthcare workers.
- Appropriate use of antibiotics.
- Enforcing legislation related to stopping the selling of antibiotics without prescription.
- Improving adherence to infection prevention and control measures.

資料來源：WHO

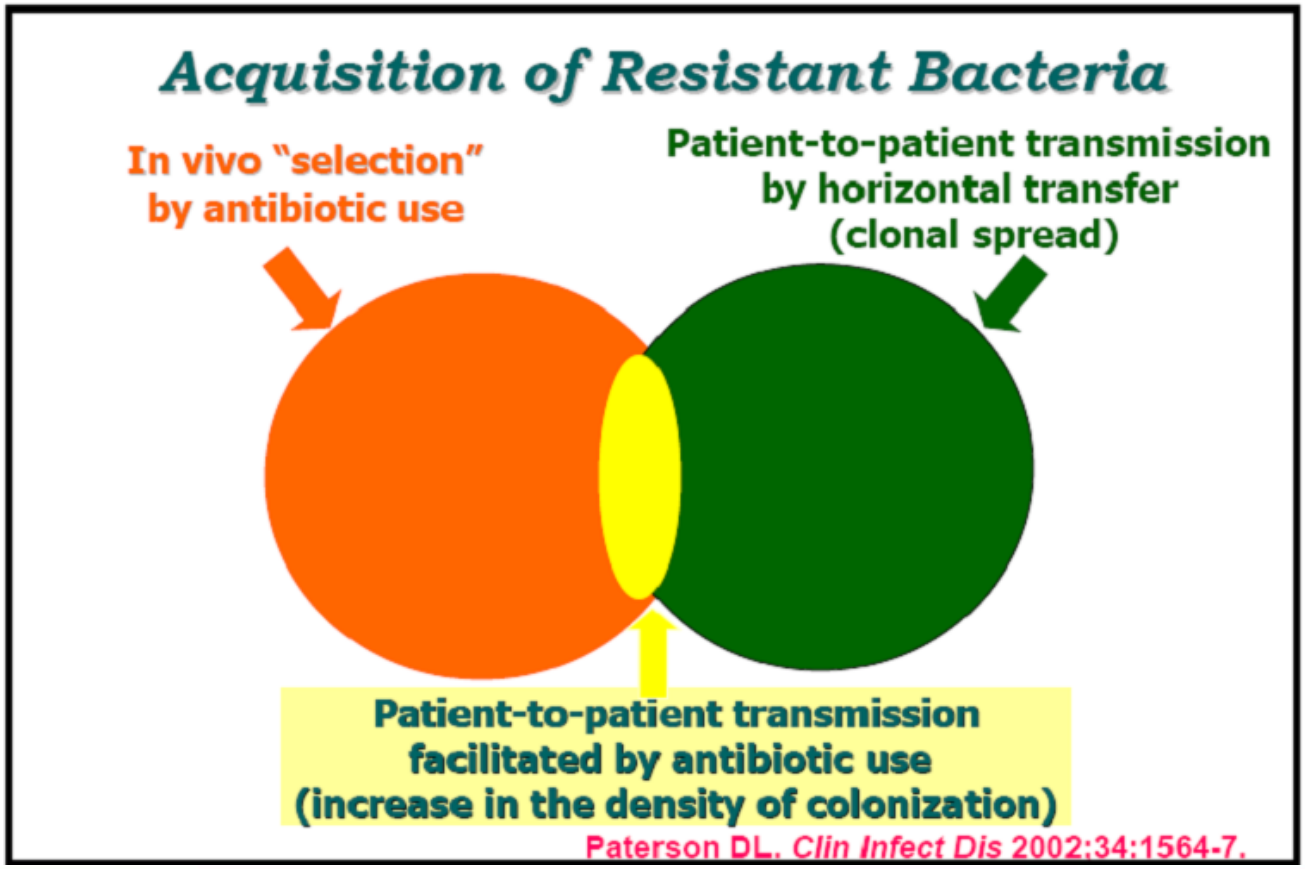
Modern Healthcare Systems



資料來源：Elsevier 2004. Infectious Diseases 2e

Management for Multidrug-resistant Organisms

- Antibiotic control ⟷ Infection control



資料來源：Paterson DL. Clin Infect Dis 2002: 34: 1564-7

Infection Control for Multidrug-resistant Organisms(1/2)

- Hand hygiene
- Standard and contact precautions (e.g., gowns, gloves)
- Cohorting of patients and staff
- Evidence-based practices to prevent device-related infections
- Environmental cleaning and disinfection
- Equipment cleaning and disinfection

資料來源：Crit Care Med 2010; 38 [Suppl.]: S345-S351

Infection Control for Multidrug-resistant Organisms(2/2)

- Identification and isolation of colonized patients
- Risk factor identification
- Active surveillance cultures
- Surveillance of microbiology results
- Outbreak investigation
- Microbiological detection methods
- Antimicrobial stewardship

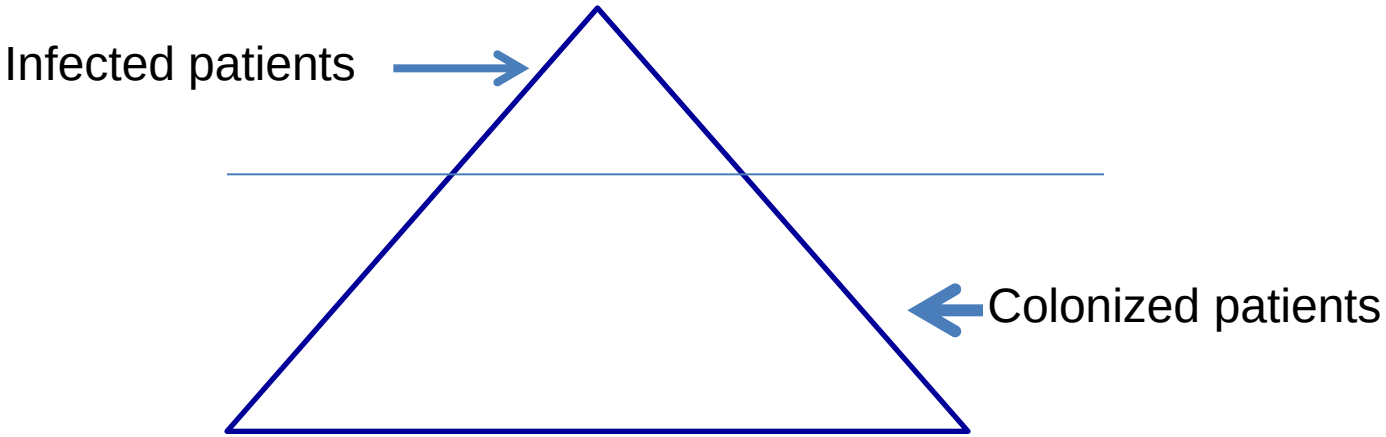
Surveillance Cultures(1/2)

- If previously unrecognized CRE cases or hospital-onset CRE infections are identified, facilities should consider surveillance cultures from patients with epidemiologic links to CRE case-patients.

- The goal of these cultures is to identify additional unrecognized CRE-colonized patients who are a potential source for transmission.

Surveillance Cultures(2/2)

- Appear to be most useful in the setting of hospital outbreaks and among patients at high risk for infection, such as patients in ICUs, immuno-compromised patients, long-term care facility residents.



Active Surveillance Cultures

當院內出現首例或院內發現多重抗藥性基因（如:KPC或NDM）群突發疫情

- 建議醫療機構針對與多重抗藥性基因（如：KPC或NDM）陽性個案有流行病學上相關的病人或其他人員，應全面進行主動篩檢監測，並送驗陽性CRE菌株至疾管署，持續至最後1例陽性個案採檢日後6個月。

醫療機構於下列狀況時，應進行主動篩檢，檢驗是否帶有多重抗藥性基因（如：KPC或NDM）。

- 若經調查後確定院內高風險區域，建議對當時該區域內所有病人進行主動篩檢。
- 於48小時內來自高風險區域（如：長照機構或已證實有CRE院內群突發醫院）之入院病人。
- 當病人須移轉至院內高風險區域（如：ICU）時。
- 當有流行病學證據指出多重抗藥性基因（如：KPC或NDM）的傳播和環境有關時，應進行環境（如：環境表面或共用的醫療設備）採檢送驗。

Contact Isolation

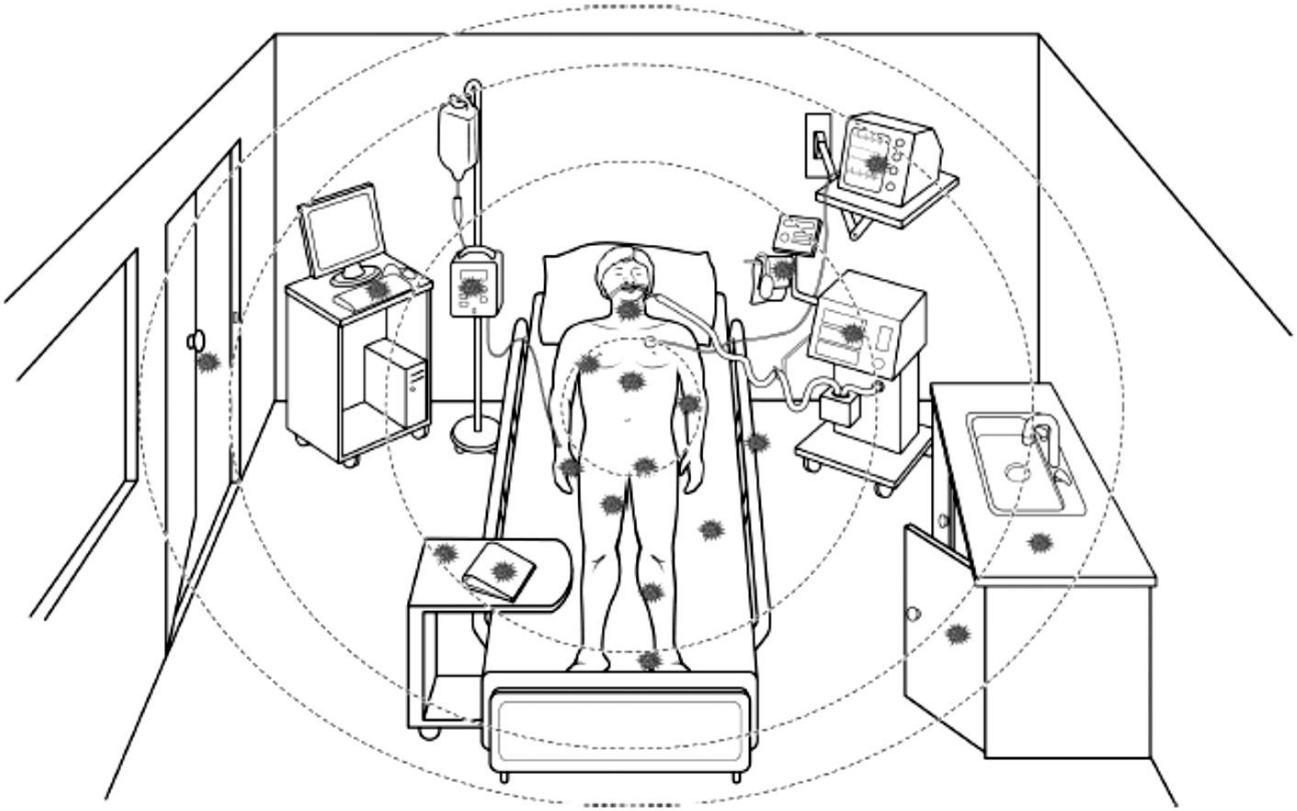
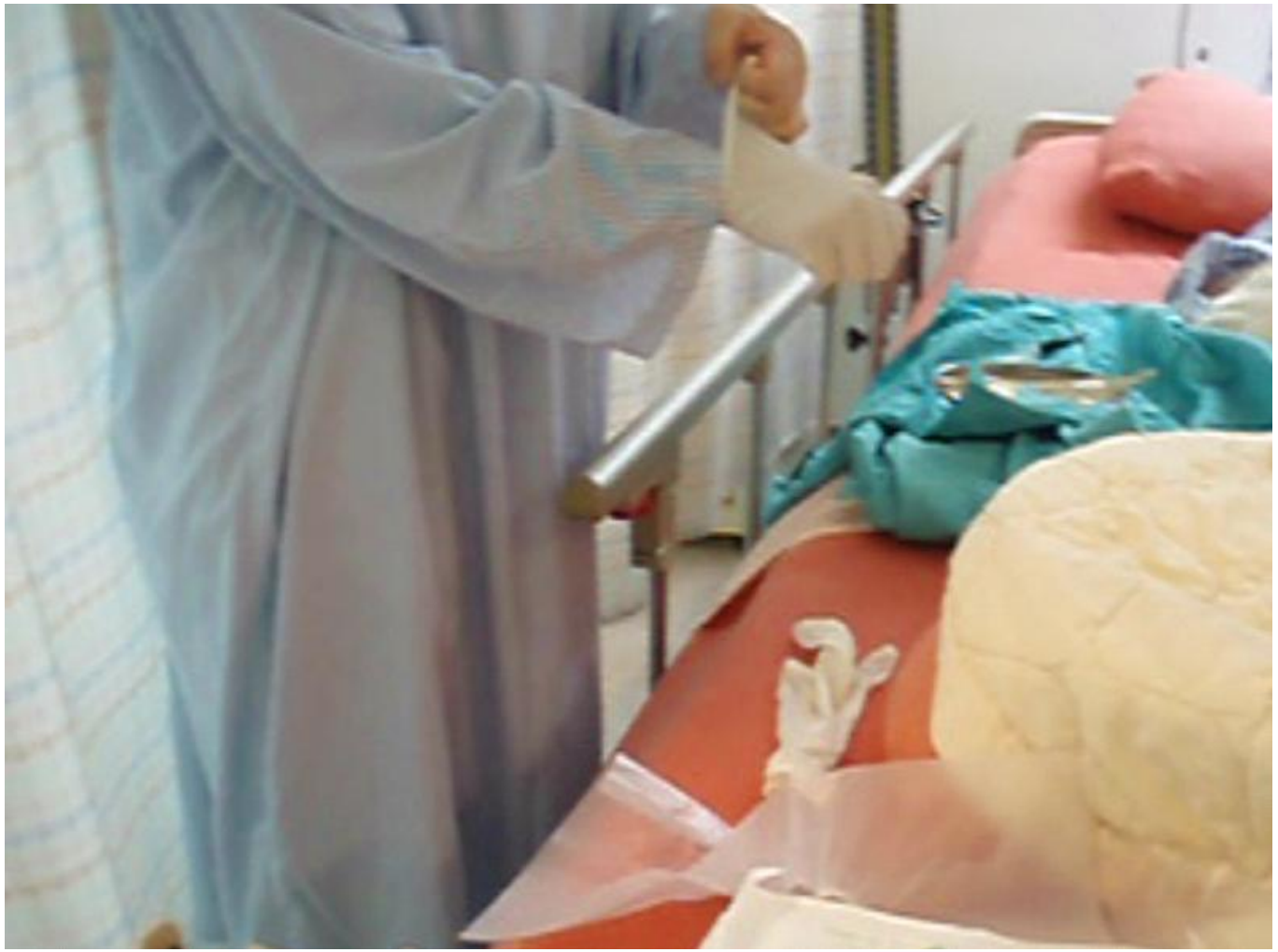


Figure 1. Patient and environmental sources of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) in an intensive care unit room. *Expanding circles* highlight the patient as the major reservoir and epicenter for MRSA and VRE. *Splotches* represent locations where MRSA and VRE are commonly found.

資料來源：Crit Care Med 2010; 38 [Suppl.]: S335-S344

Contact Isolation: Gloves



資料來源：臺北醫學大學附設醫院感染管制室

用物之感染管制(1/2)

乾洗手劑

- 為方便洗手，請於病室內放置酒精乾洗手液，以利洗手。

固定的聽診器、血壓計

- 醫療儀器應單獨使用，醫護人員盡量不要使用自身的聽診器，血壓計放於床尾，需與感染性污衣桶及感染性垃圾桶間隔開，勿緊貼於旁，保持適當距離，另每天需以75%酒精消毒，擦拭方式將清潔溶液噴於擦手紙上，再以擦手紙擦拭血壓計及壓脈帶。

顳溫計

- 使用專用護套碰觸病人，使用後立即以75%酒精消毒。

用物之感染管制(2/2)

隔離衣

- 放於靠近抗藥性菌種病人床位旁，盡量單次使用，若需重覆使用，則懸掛隔離衣時請勿堆疊碰觸在一起，懸掛方式請將污染面包於內懸掛，三班定期更換。

感染性污衣桶及感染性垃圾桶（置於床尾靠牆壁處）

- 垃圾桶或污衣桶須加蓋，避免有溢出情形。

隔離用物擺設

換藥車

- 使用後之換藥車遇血體液噴濺，立即以75%酒精或漂白水擦拭消毒，換藥車內的垃圾立即處理。

其他可能共用之物品

- 如輪椅、推床等，使用後需以75%酒精或漂白水擦拭乾淨後，才能再使用。

床位安排(1/2)

- 外院加護病房(ICU)或呼吸照護病房(RCW)呼吸器依賴之病人，轉入本院加護病房時，因可能帶有多重抗藥性菌，收治時應實施接觸隔離措施，避免於照護過程交叉感染。
- 多重抗藥性微生物的病人應儘量予獨立房間。
- 病房內若有數位多重抗藥性微生物感染病人時，床位應予集中，並儘可能安排同一組護理人員照護，而此組護理人員應避免同時照顧其他無多重抗藥性微生物感染之病人。
- 具有抗藥性菌種病人若住非單獨病室時，請盡量將安排在病室最內側靠窗戶之床位。

床位安排(2/2)

- 多重抗藥性微生物感染病人，於轉院或移轉至護理之家、療養院、RCW等機構時，應於出院病摘詳細記載為抗藥性菌種感染病人，以提醒其他機構執行院感及備有相關配套措施。
- 抗藥性菌種病人與免疫不全病人簽床原則，請參閱傳染性病人簽床流程。
- 當消除單位環境傳染源的努力失敗時，應將單位淨空，做環境評估及加強清潔消毒工作。

Antimicrobial Stewardship

- 審慎地使用抗微生物製劑
  - 探討抗微生物製劑在多重抗藥性微生物問題的角色，以加強控制措施。視需要，管制及改善抗微生物製劑的使用。重點的抗生素包括：
    - Glycopeptide類藥物，第三代的頭孢黴素(Cephalosporins)，抗厭氧菌藥物，此部分針對於減少VRE。
    - 第三代頭孢黴素，此部分針對用於減少ESBLs細菌。
    - 恩氟類(Quinolones)
    - 碳醯胺基類(Carbapenems)抗微生物製劑

Antimicrobial Stewardship Programs

- Ensuring the proper use of antimicrobials to provide the best patient outcomes
- Lessen the risk of adverse effects
- Promote cost-effectiveness
- Reduce or stabilize levels of resistance

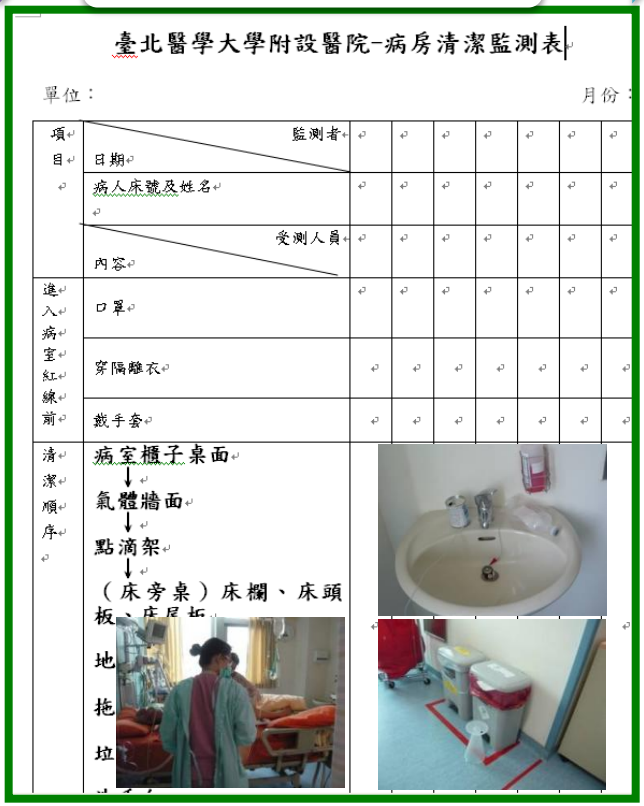
醫院抗生素小組

- 每月定期會議
- 每月抗生素耗用量監測及分析
- 每半年進行抗藥性趨勢與抗生素用量分析
- 抗生素管制措施及使用檢討
- 每月臨床抗生素使用案例討論

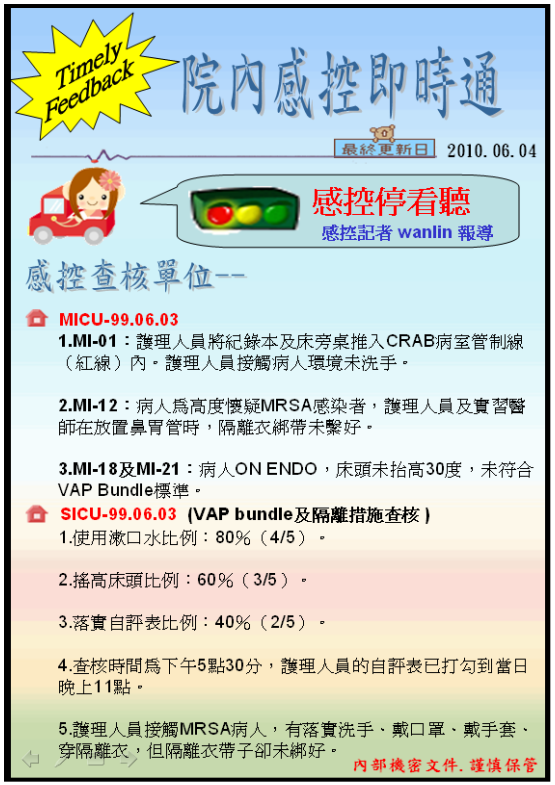
加護病房多重抗藥性細菌異常事件處理過程

宣導與教育

查核



即時回饋



資料來源：臺北醫學大學附設醫院感染管制室

Infection Control for CRE

- Hospitalized patients infected or colonized with carbapenemase-producing bacteria should be placed on contact precautions.
- Other standard measures: as hand hygiene, minimizing the use of invasive devices, and antimicrobial stewardship.
- Screening high-risk patients to detect rectal colonization.
- Active surveillance.

Culture Change 運用實例

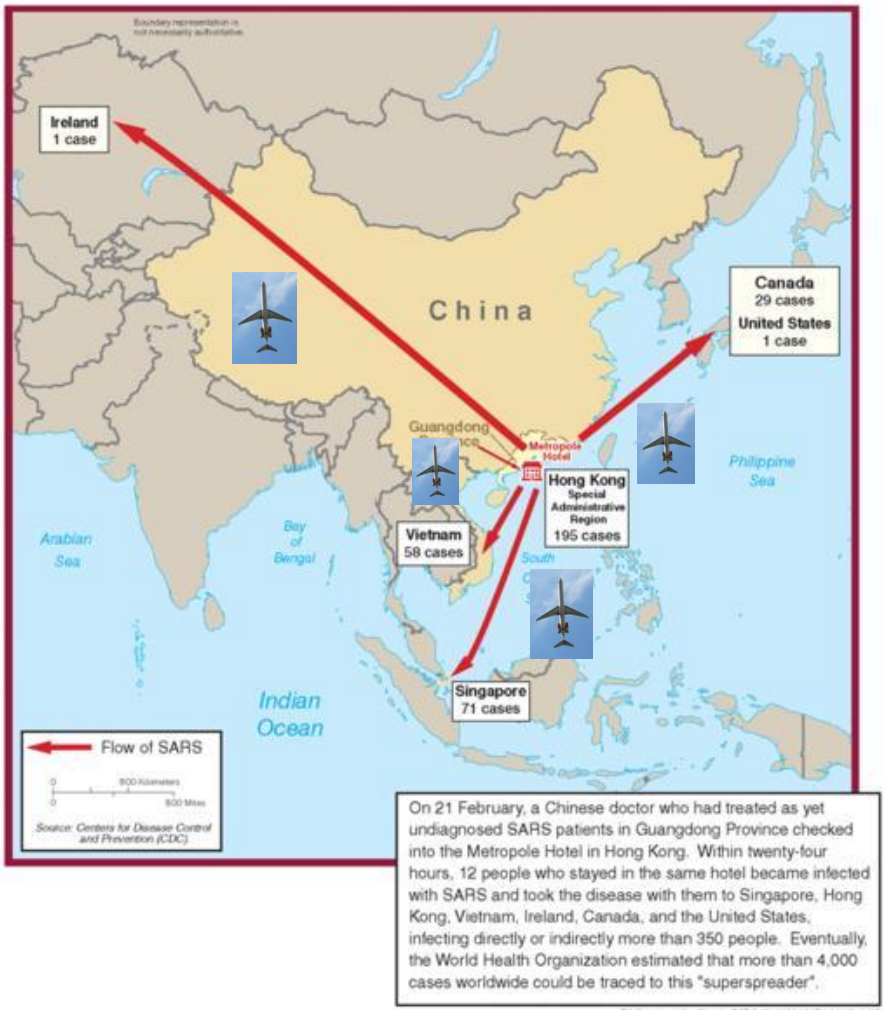
某位醫師總是刻意將有多重抗藥性細菌感染的病人排在查房名單的最後一個，以免將這些病人的病菌帶到下一個病人身上。

ICU護理人員在其上班時段中用消毒水擦拭病人床桿數次，以避免病人觸碰到可能帶有病菌的床桿而感染。

有位醫師決定不穿醫師袍和長袖，也不打領帶，以降低多重抗藥性細菌的傳播（長袖子、衣角與領帶容易碰到病人，又不容易隨時消毒，成為傳播感染的媒介）。

傳染病無國界

- Infectious diseases do not respect international borders



資料來源：Intelligence community assessment 2003-09

課程結束