Carbapenem-Resistant *Acinetobacter baumannii* : Update on Molecular Epidemiology, Treatment and Infection Control

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Outline

1. Introduction & Background
2. Carbapenem Resistant Mechanism & Epidemiology
3. Treatment Options
4. Infection Control

Introduction & Background

Acinetobacter species are aerobic gram-negative bacilli are ubiquitous in natural (soil, water) and hospital environment

- Greek [α + κίνητο + βακτηρ(ία)] : *nonmotile* rod (不動桿菌)
- *Acinetobacter baumannii*: accounts for most infection in humans

CDC, Public Health Image Library

Early reports in war wound (Korean war and Vietnam war)

TABLE III. *Organisms Isolated by Blood Culture—Series II.*

Patient	Aerobic	Anaerobic
A	Staphylococcus, non-hemolytic	Negative
	Corynebacterium hofmanni	
B	Staphylococcus*	Negative
	Bacillus species	
	Staphylococcus, non-hemolytic	
C	Bacillus species	Negative
D	Bacillus species	Negative
E	Achromobacter	Negative

Table 2.—Frequency of Bacterial Isolates From Blood Cultures

Enterobacter group	21
Mimeae-*Herellea-Bacterium-Alcaligenes*	14
Serratia marcescens	4
Pseudomonas aeruginosa	4
Proteus mirabilis	3
enterococci	1
Staphylococcus aureus	1

Ann Surg. 1955; 141(3): 366–368. JAMA. 1972;219(8):1044-1047.

There is no escape from the ESKAPE pathogens

- Hospital Acquired Infections
- The CDC estimates antibiotic resistant ESKAPE pathogens cause over 2 million illnesses and approximately 23,000 deaths per year.

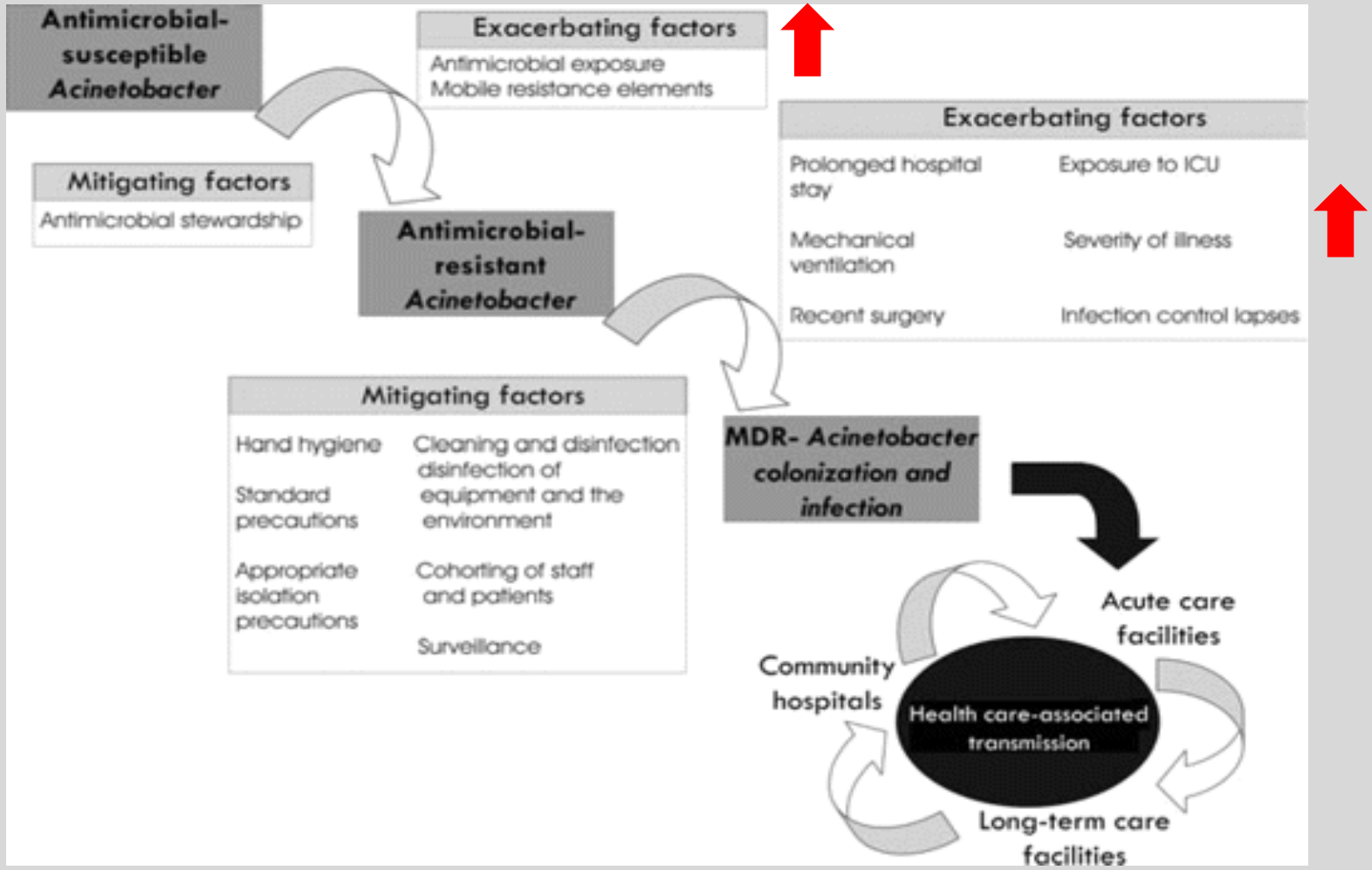
Intrinsic resistance to several antibiotics

Organisms	Ampicillin	Amoxicillin-Clavulanic acid	Ampicillin-sulbactam	Ticarcillin	Ticarcillin-clavulanic acid	Piperacillin	Piperacillin-tazobactam	Cefazolin, Cefalothin Cefalexin, Cefadroxil	Cefotaxime	Ceftriaxone	Ceftazidime	Cefepime	Aztreonam	Ertapenem	Imipenem	Meropenem	Ciprofloxacin	Chloramphenicol	Aminoglycosides	Trimethoprim	Fosfomycin	Tetracyclines	Tigecycline	Polymyxin B/Colistin
Acinetobacter baumannii, *Acinetobacter pittii*, *Acinetobacter nosocomialis* and *Acinetobacter calcoaceticus* complex	R	R	Note[1]					R	R	R			R	R						R	R	R[2]	Note[2]	

[1] *Acinetobacter baumannii* may appear to be susceptible to ampicillin-sulbactam due to activity of sulbactam with this species.
[2] *Acinetobacter* is intrinsically resistant to tetracycline and doxycycline but not to minocycline and tigecycline.

EUCAST

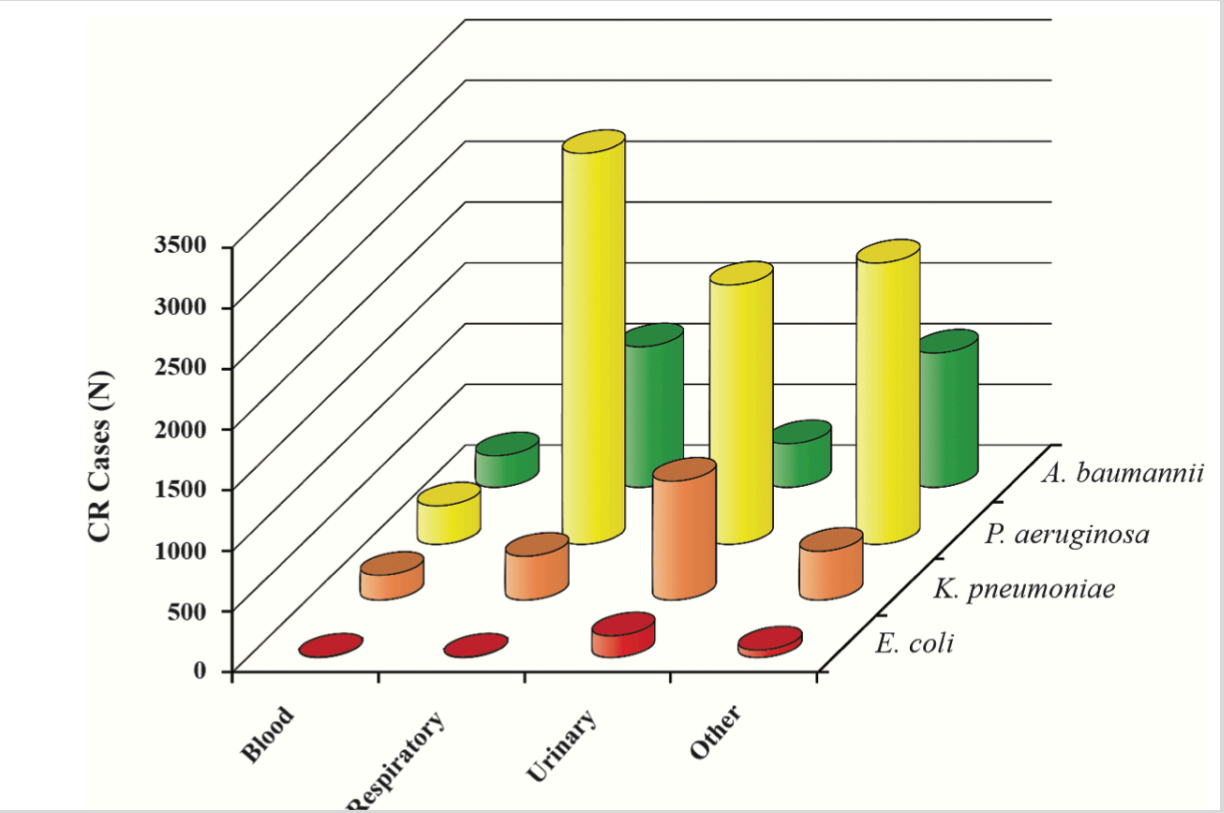
From susceptible to resistant



CID. 2008; 46(8): 1254–1263

Urgent threat to human health

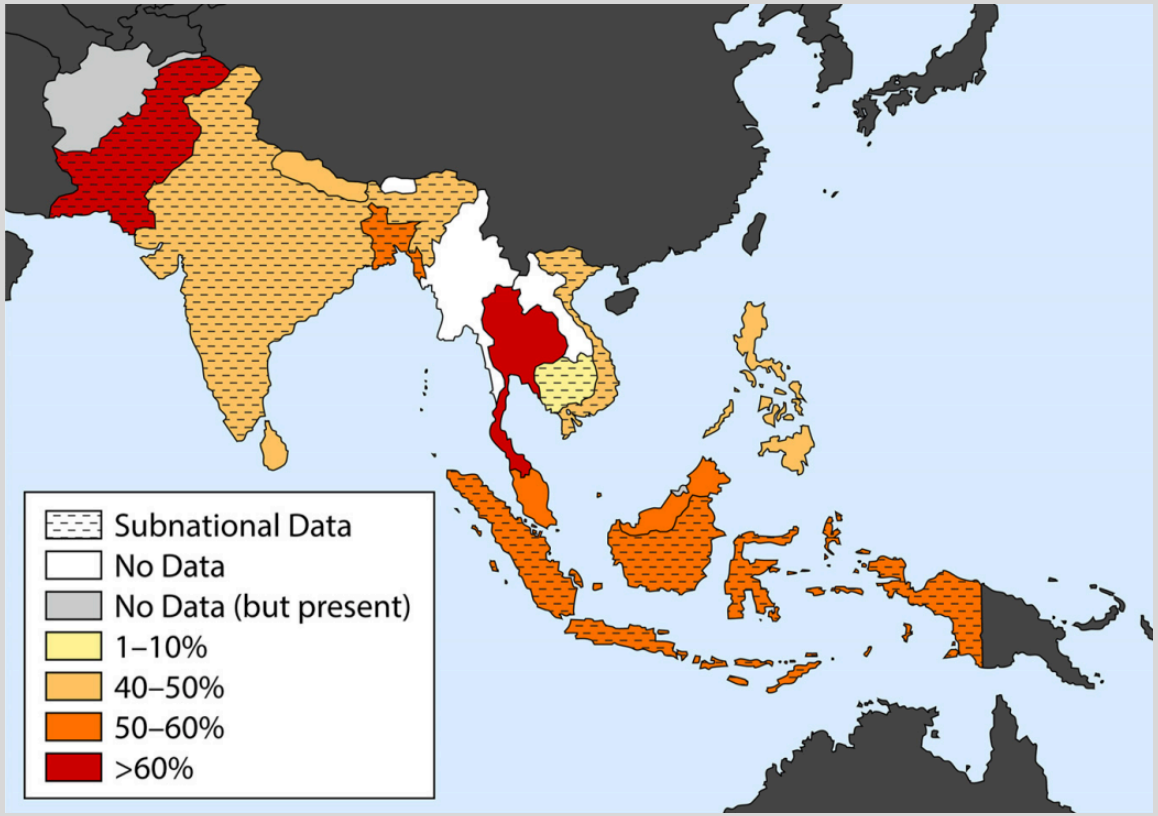
Number of Infections caused by Carbapenem resistant pathogens



CID 2019:69 (Suppl 7)

Carbapenem Resistant Mechanism & Epidemiology

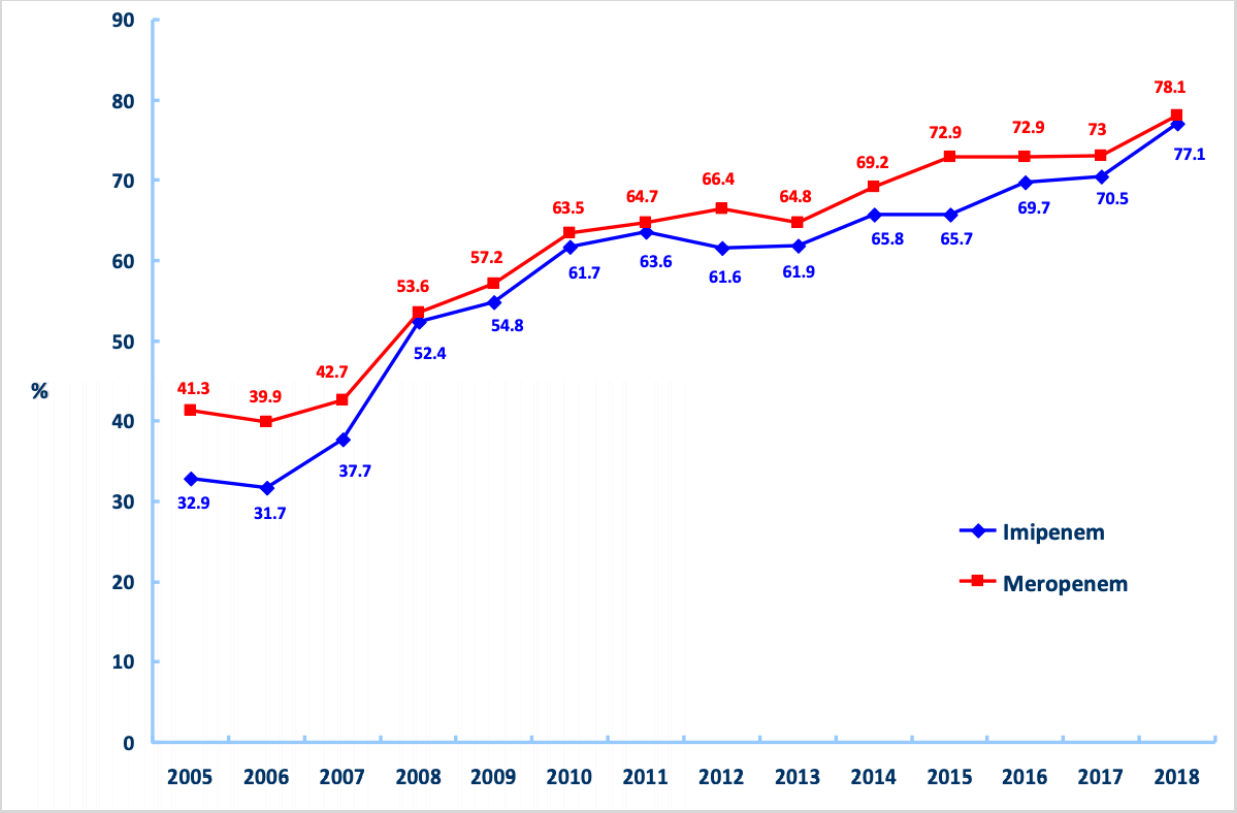
Estimated prevalence of carbapenem-resistant Acinetobacter baumannii in South and Southeast Asian countries



CMR, 2017, 30(1), 1-22

Rapid rising of CRAB in mainland China

China antimicrobial surveillance network (CHINET) data



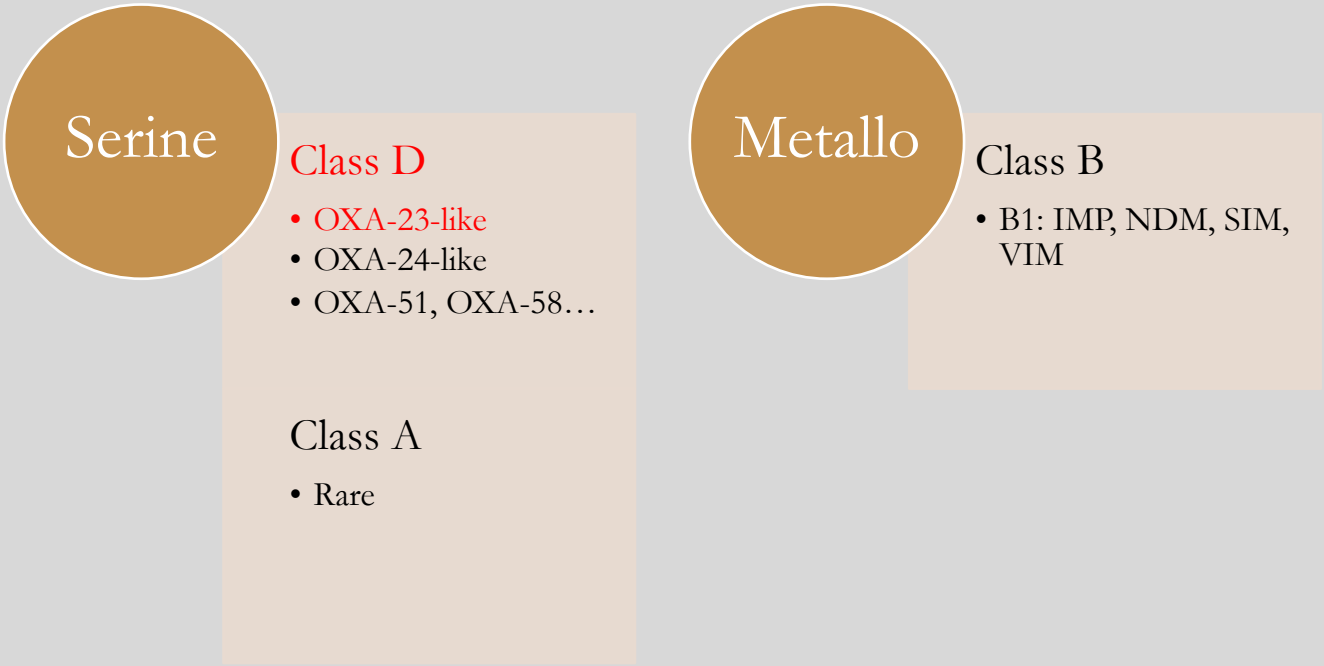
European Journal of Clinical Microbiology & Infectious Diseases 38.12 (2019): 2275-2281.

Mechanisms of Carbapenem resistant in *Acinetobacter baumannii*

- Carbapenem-inactivating enzymes
- Reduced access to bacterial targets
- Mutations that change targets or cellular functions

Carbapenem-inactivating enzymes

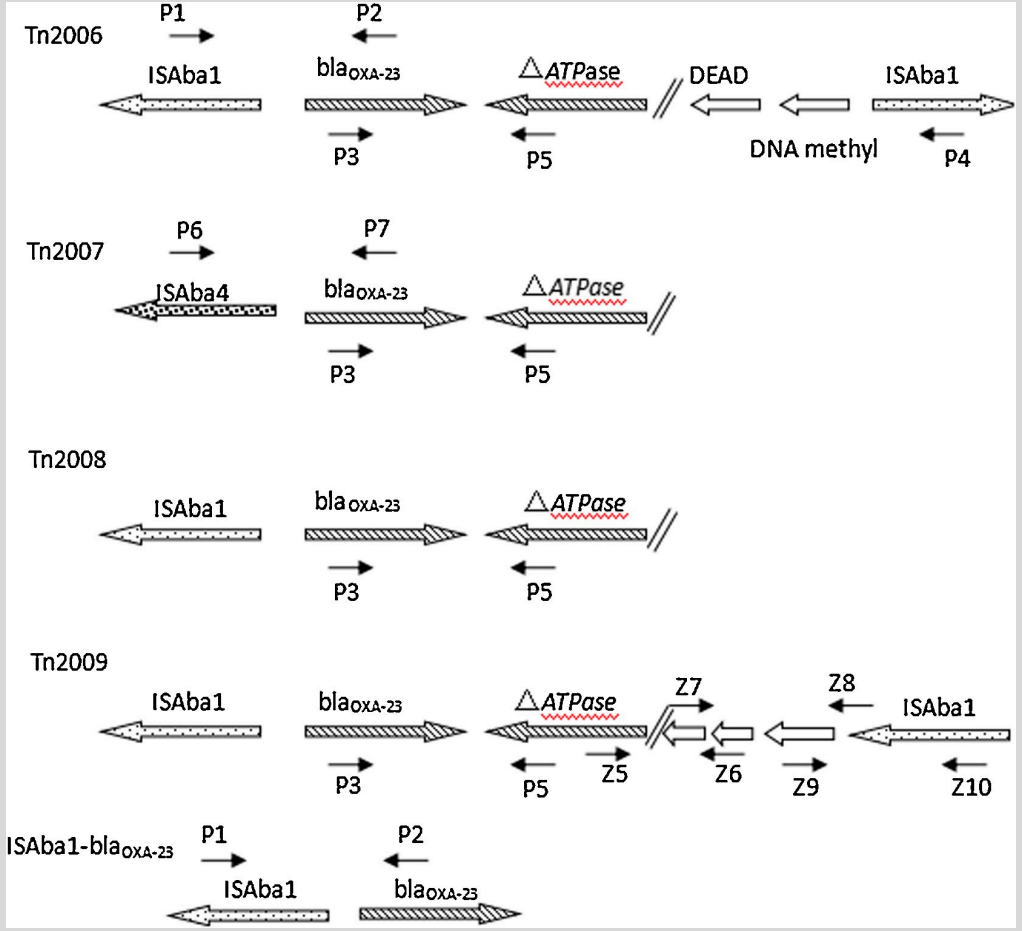
- Native chromosomal enzyme: OXA-51(low-level expression, upregulated by IS*Aba*1/9)
- Acquired carbapenemase
- Hong Kong study, 80% produce OXA-23-like enzyme, while only 10% with the structure of IS*Aba*1 + OXA-51. Another study 100% OXA-23-like enzyme
- Mainland China study, OXA-23-linge enzyme is predominant



MDR 2019; 25(8), JHI 74.4 (2010): 358-364, EID 16 (2010):35-40

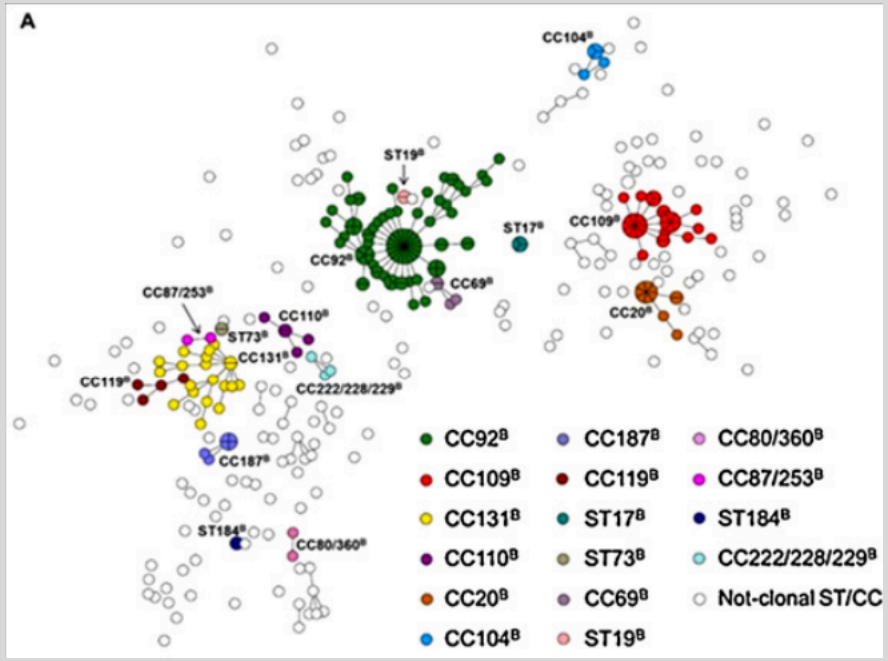
Mobile genetic elements related to OXA-23

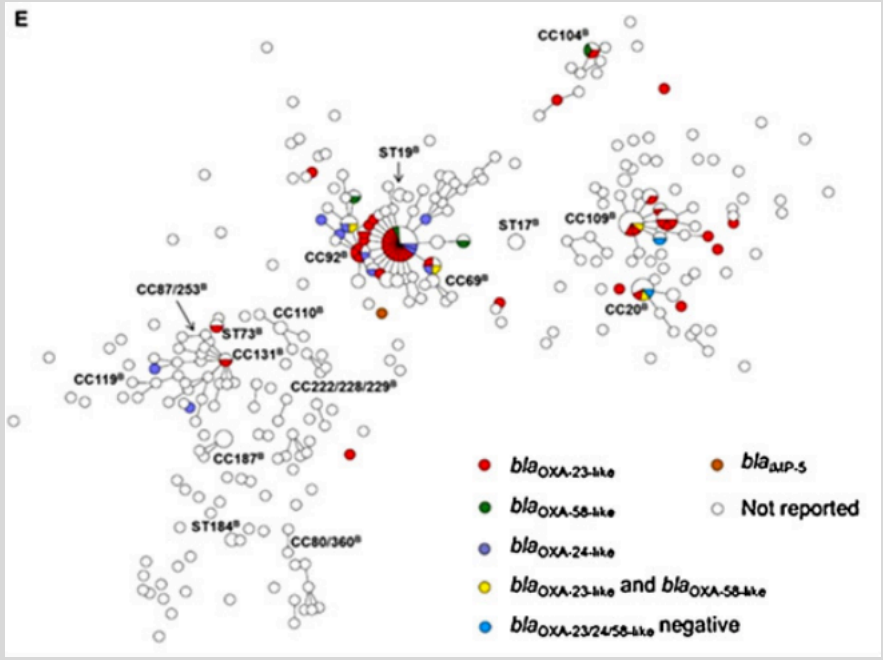
- Mobilized to Chromosome or Plasmid
- Can have >1 copy numbers
- Mainland China: Tn2009
- Taiwan, other countries: Tn2006
- Short reads sequencing is not accurate due to repeat regions of IS*Aba*
  - Tn2009 discovered in 2011 corrected in 2018 by PacBio sequencing
- HK: no data



AAC 2015;59(4), Journal of global antimicrobial resistance 17 (2019): 84-89, JAC 74.4 (2018): 1153-1155.

Global Clone of CRAB



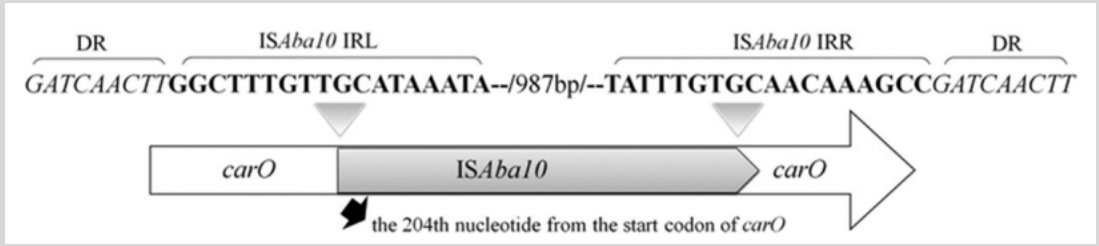


Global dissemination of CC92, same in HK

Drug Resistance Updates 15.4 (2012): 237-247. Microbial Drug Resistance 2019; 25(8)

Other mechanisms

- Reduced access
  - Interruption of Outer membrane proteins (OMPs): CarO, OmpW



- Mutations
  - Efflux pumps: AdeABC, AdeFGH, AdeIJK
  - e.g. AdeB(F136L&G288S)→Meropenem MIC>8 ug/ml
    PBP3

AAC 55.1 (2011): 361-363. Microbial genomics 4.3 (2018).

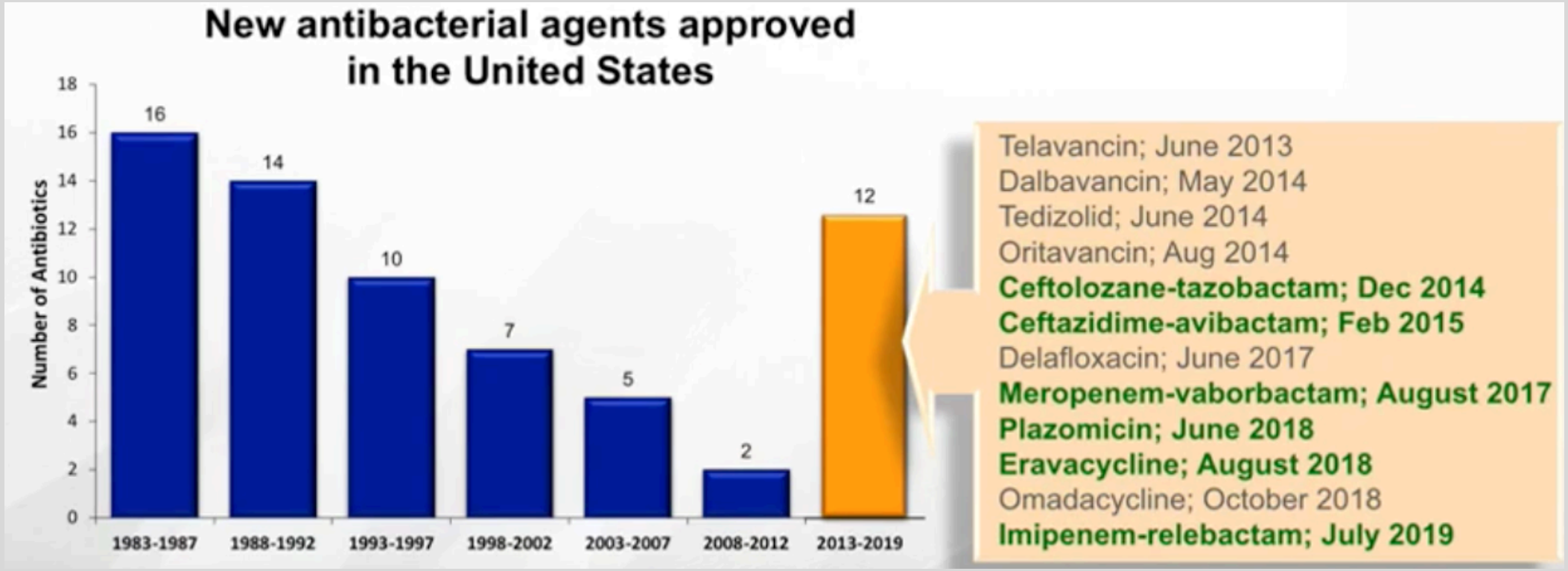
Treatment Options

Limitations of current therapeutic options

Issue	Colistin	Tigecycline	Minocycline	Amikacin	Sulbactam
Pharmacokinetic issues					
Narrow therapeutic spectrum	✓				
Low or inconsistent drug levels					
Plasma	✓	✓			
Lung	✓	✓			
Urine		✓			
Toxicity					
Nephrotoxicity	✓			✓	
Neurotoxicity	✓				
Resistance					
High resistance rates		✓	✓	✓	✓
Heteroresistance	✓				
Breakthrough	✓	✓			
Only in combination			✓	✓	✓
Increased mortality		✓			

AAC 63.1 (2019): e01110-18.

New antibiotic agents approved

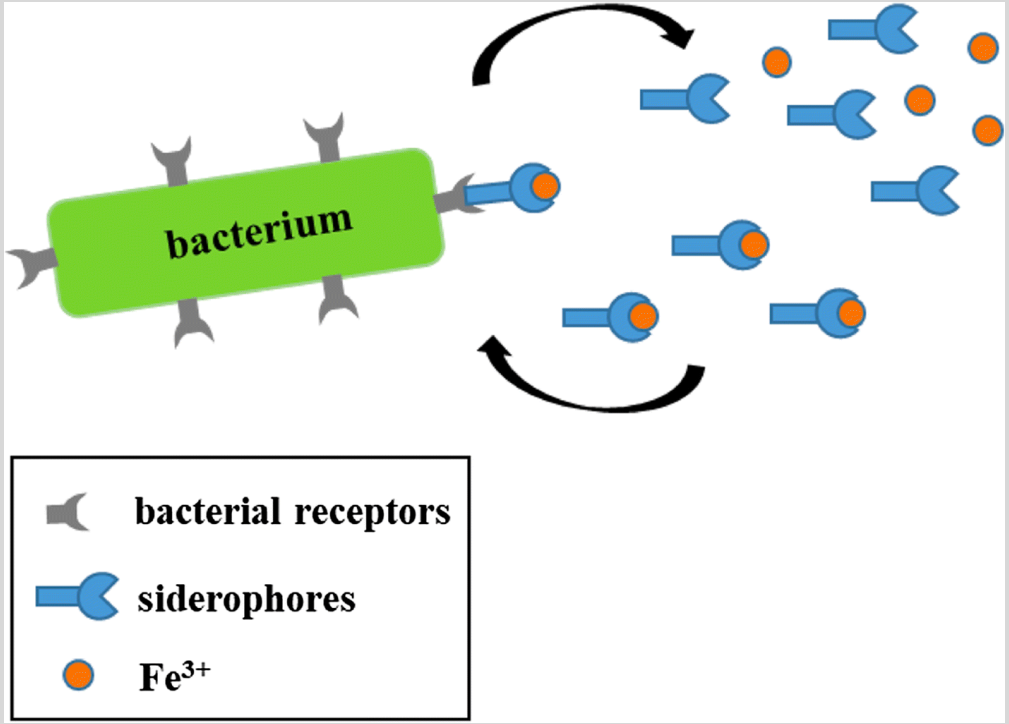


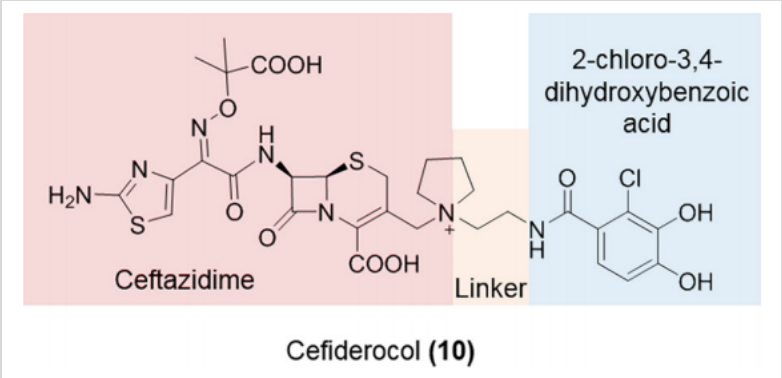
New treatment options for CRAB

1. Siderophore cephalosporins: Cefiderocol
2. Tetracycline: Eravacycline

Cefiderocol, first siderophore cephalosporins

- Bypass the bacterial porin channel, using iron-transport system
- For CRAB: MIC_{90} <= 1ug/ml





Clinical microbiology reviews 31.2 (2018): e00077-17.

Comparative Efficacy of Cefiderocol & Imipenem-cilastatin for cUTIs

- multicentre, double-blind, non-inferiority trial
- Cure: 183 [73%] of 252 vs 65 [55%] of 119
- Approved by FDA last month: for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis , caused by the following: susceptible Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex.
- CRAB: ongoing

Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens (CREDIBLE - CR)

Recruitment Status : Completed
First Posted : March 21, 2016
Last Update Posted : April 25, 2019

Sponsor:
Shionogi

Information provided by (Responsible Party):
Shionogi Inc. (Shionogi)

SHIONOGI

Open Forum Infect Dis 4:S537–S538.

Eravacycline

- Novel fluorocycline of tetracycline family
- Active against colistin-resistant and ceftazidime-avibactam-resistant strains
- CRAB: MIC_{50} = 0.5 ug/ml, MIC_{90} = 1 ug/ml
- Production of OXA enzyme did not change the MICs
- FDA approved for treatment of cIAI (Complicated Intra-abdominal Infections)

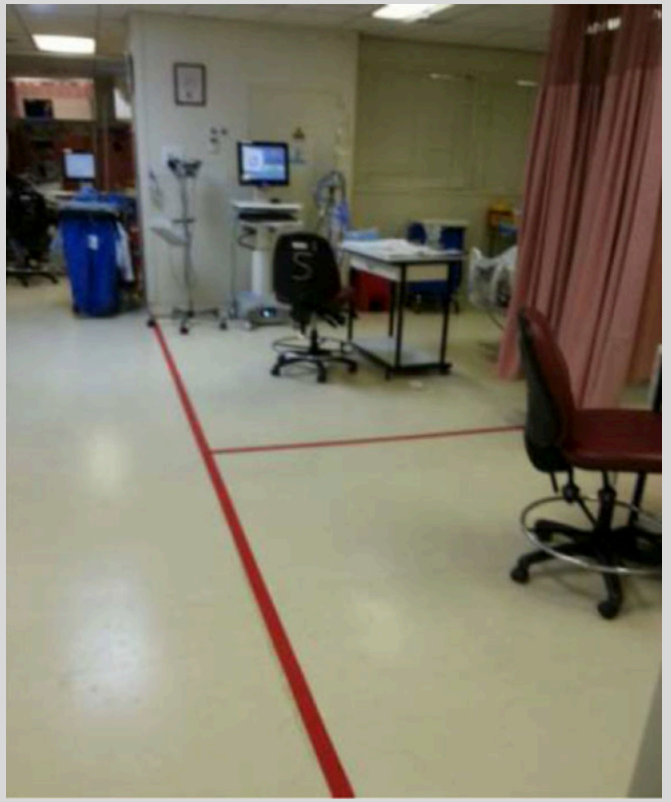
New therapeutic options

Drug	Preclinical	Phase I	Phase II	Phase III	FDA approved
Siderophore cephalosporins					
Cefiderocol	✓	✓	✓	✓	✓
Others					
GSK-3342830	✓	-[a]	-	-	-
Fimsbactin plus daptomycin	✓	-	-	-	-
GT-1	✓	-	-	-	-
Tetracyclines					
Eravacycline	✓	✓	✓	✓	✓
TP-6076	✓	✓	-	-	-

Infection Control

Intervention to control ICU CRAB outbreak

- On 31 May 2015, two ICU patients died simultaneously with CRAB
- **Aggressive Intervention**
  - Empty the ICU, clean 16h per day for 3 days
  - Assessed by ATP detection
- **Prevent recurrence**
  - Virtual wall: Gloves (touch patient, bed), Hand hygiene
  - Stop shared trolleys, portable computers
  - New cleaning personnel, disposable cloth, replace 2000 ppm sodium hypochlorite every 24h
  - Increased hand hygiene observations and inspections, education
  - Screening cultures, ATP detection continued



Critical Care (2018) 22:319

CRAB daily prevalence

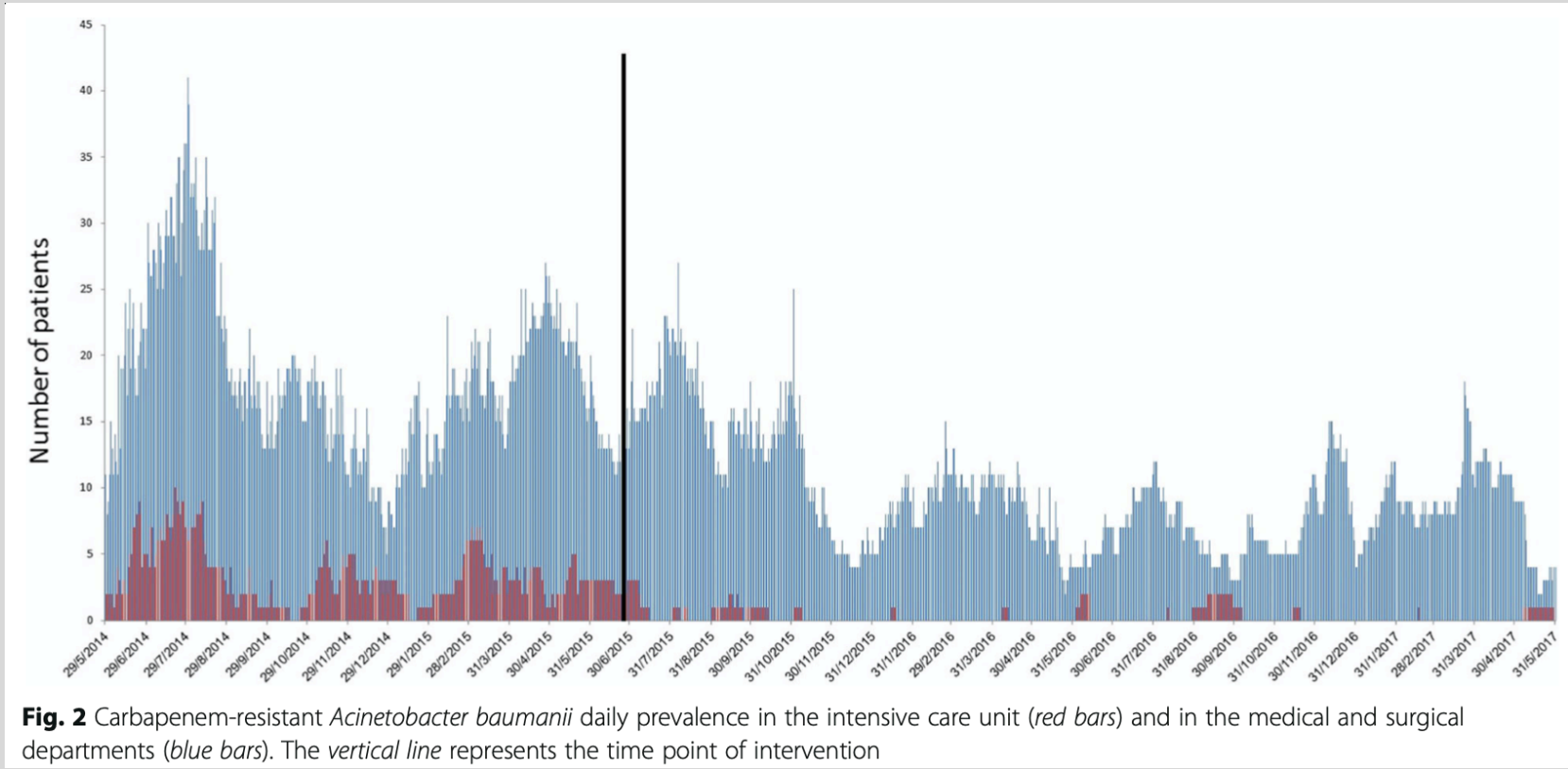
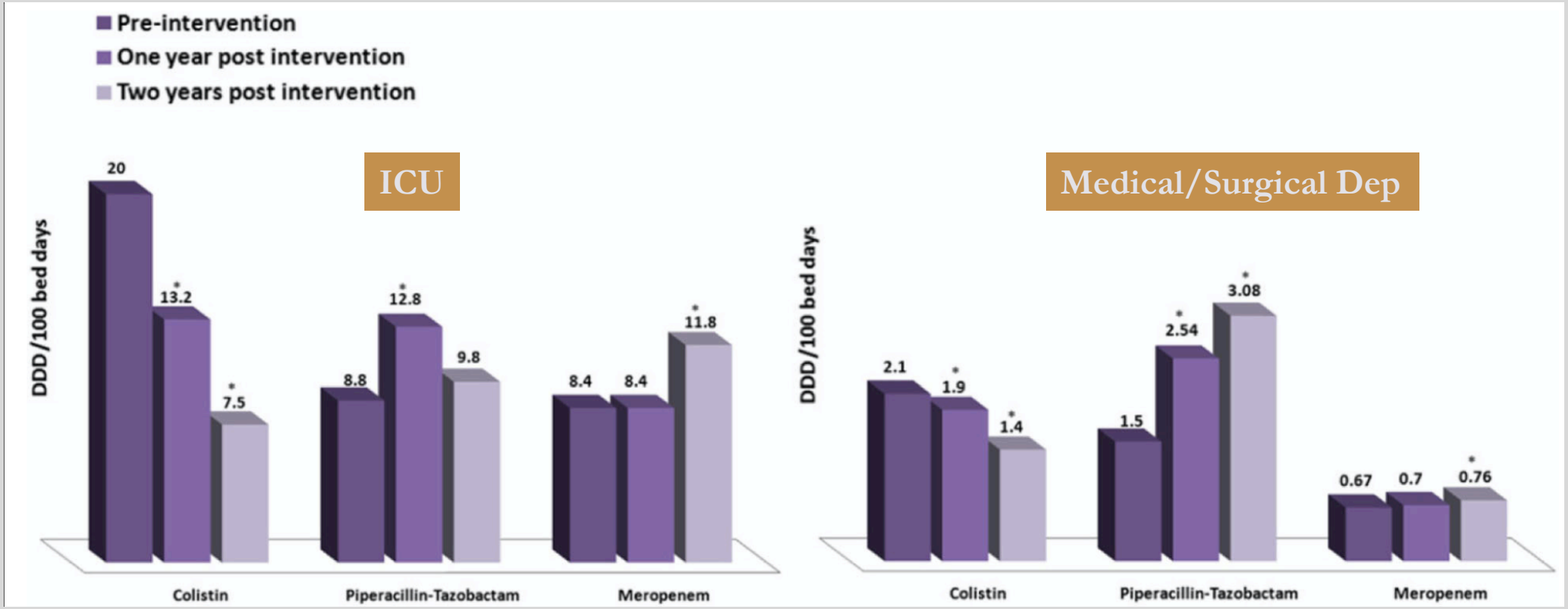


Fig. 2 Carbapenem-resistant *Acinetobacter baumanii* daily prevalence in the intensive care unit (*red bars*) and in the medical and surgical departments (*blue bars*). The *vertical line* represents the time point of intervention

Before and after intervention

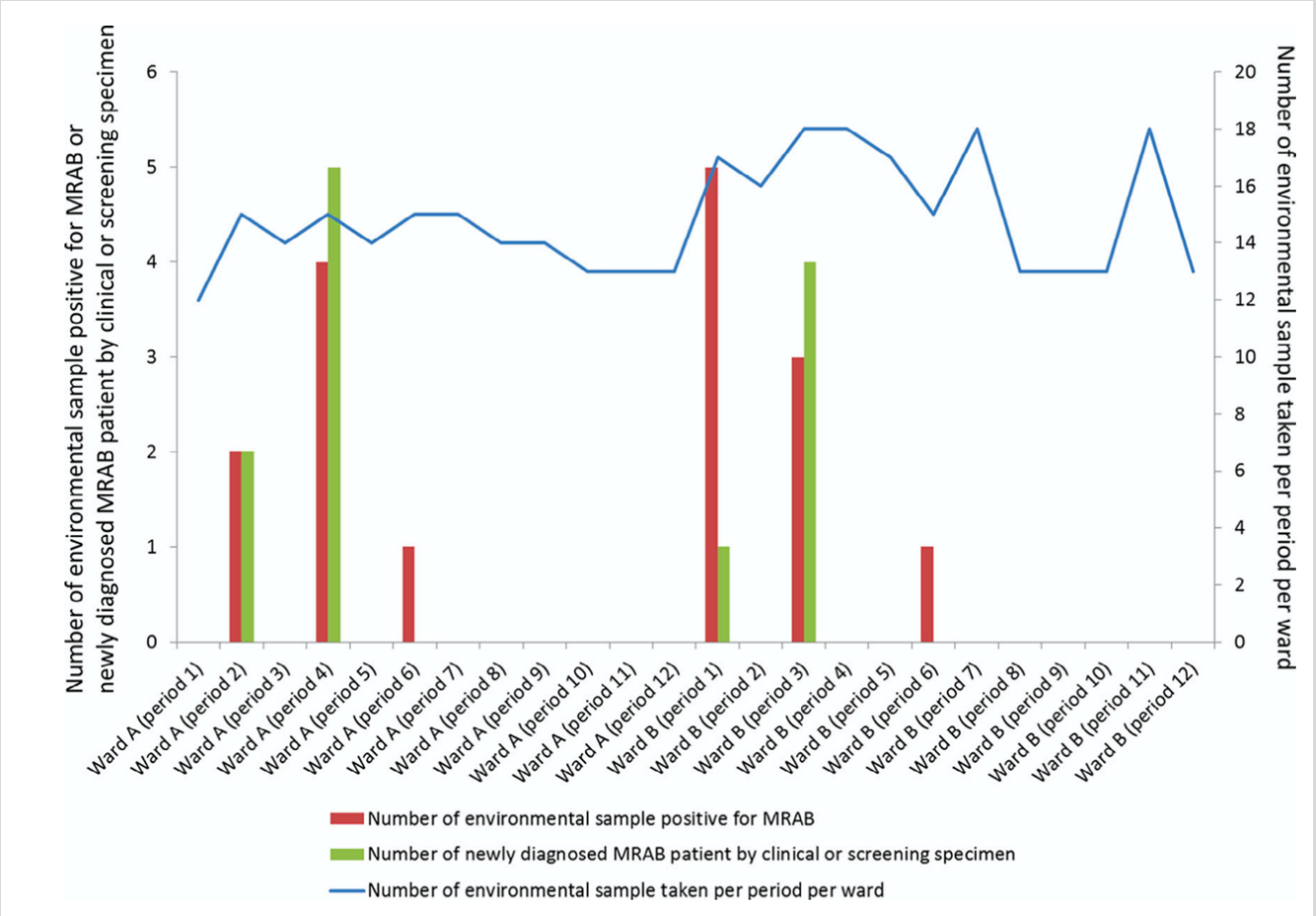
	Before intervention (period 1)	One year postintervention (period 2)	Two years postintervention (period 3)
ICU admissions (*n*)	513	516	537
Age (years)	61 ± 20.2	50 ± 21.7	59 ± 21.2
Gender (male)	277 (54%)	300 (58.1%)	306 (57%)
APACHE II score	18.3 ± 8.1	18.4 ± 8.1	18.3 ± 8.0
Median ICU length of stay (days)	3 (2–6)	3 (2–7)	3 (2–6)
ICU mortality	58 (11.3%)	52 (10%)	50 (9%)
CRAB patients			
CRAB ICU acquisition[a]	54.6 (*n* = 28)	1.9 (n = 1)[b]	5.6 (*n* = 3)[b]
CRAB carriers discharged alive from ICU to hospital wards[a]	58.5 (*n* = 30)	1.9 (n = 1)[b]	7.4 (*n* = 4)[b]
CRAB ICU admission prevalence[a]	56.5 (*n* = 29)	5.8 (n = 3)[b]	13.0 (*n* = 7)[b]
Median ICU length of stay (days)	13 (5–22)	7 (3–28)[c]	
Median time from ICU admission until CRAB acquisition (days)	7 (4–11)	4 (3–32)[c]	
CRAB hospital mortality	31/57 (54%)	4/4 (100%)	6/10 (60%)
Medical and surgical wards			
Admissions (*n*)	39,444	41,006	44,113
Hospital wards CRAB prevalence[a] (clinical cultures)	4.4 (*n* = 173)	2.4 (*n* = 99)[b]	2.5 (*n* = 111)[b]

Antibiotics usage pre/post intervention



Control MRAB, HK practice

- Environment surveillance as a marker for enhanced Infection control
- Correlated with MRAB-positive specimen
- Compared with nonintervention ward:
  0.55 vs 2.28 infection per 1,000 patient days (p = 0.044)



American Journal of Infection Control 46 (2018) 60-6

Conclusion

- CRAB is a great threat to healthcare patients with limited treatment options
- OXA-23-like enzyme is the most prevalent carbapenemase, transmitted with specific insertion sequences
- Genetic environment of CRAB in Hong Kong is not well studied
- New antibiotics are not fully studied in clinical patients with CRAB, limited to certain infections
- Routine patient & environment surveillance and infection control practices are critical in controlling CRAB

Thank you