CRE 治療與隔離措施

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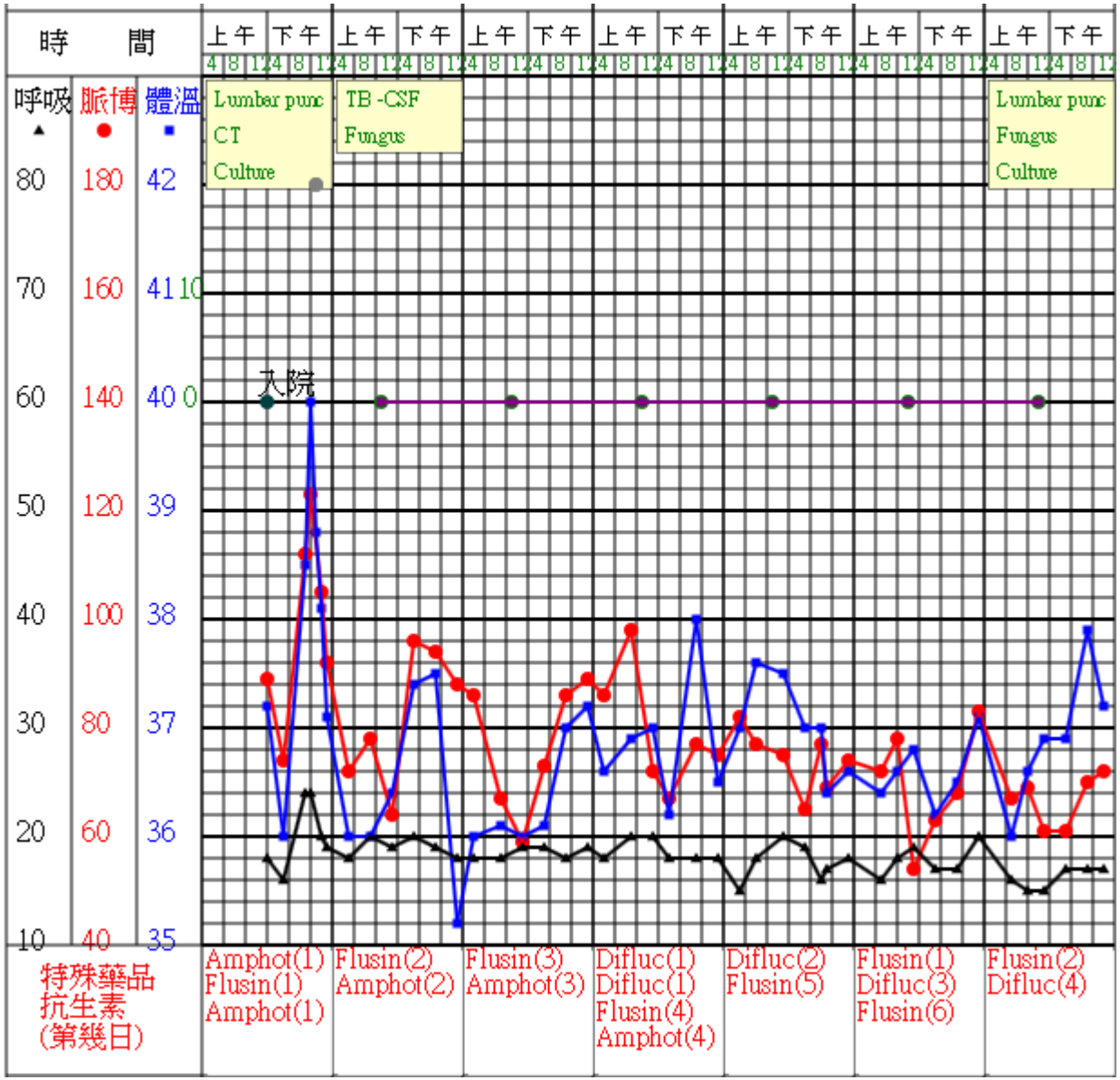
Case presentation

- 35 years old MSM, admitted due to intermittent fever and facial erythema for 1 week
- Diagnosis: HIV in AIDS with cryptococcus meningitis
- Initial CD4: 17 , VL: 249000 copies/ml
- Start amphotericin B and flucytosine-then switch to fluconazole 800mg and flucytosine days later due to skin rash developed to amphotericin B

Case presentation

- Fever developed 23 days after hospitalization
- Start with empirical ceftriaxone intravenously with amikacin st.
- Blood culture: CRE (K.P) and *Acinetobacter. Junii*
- Switch to meropenem prolong infusion and levofloxacin
- Fever subsided
- Also had cryptococcus related IRIS and control with steroid well.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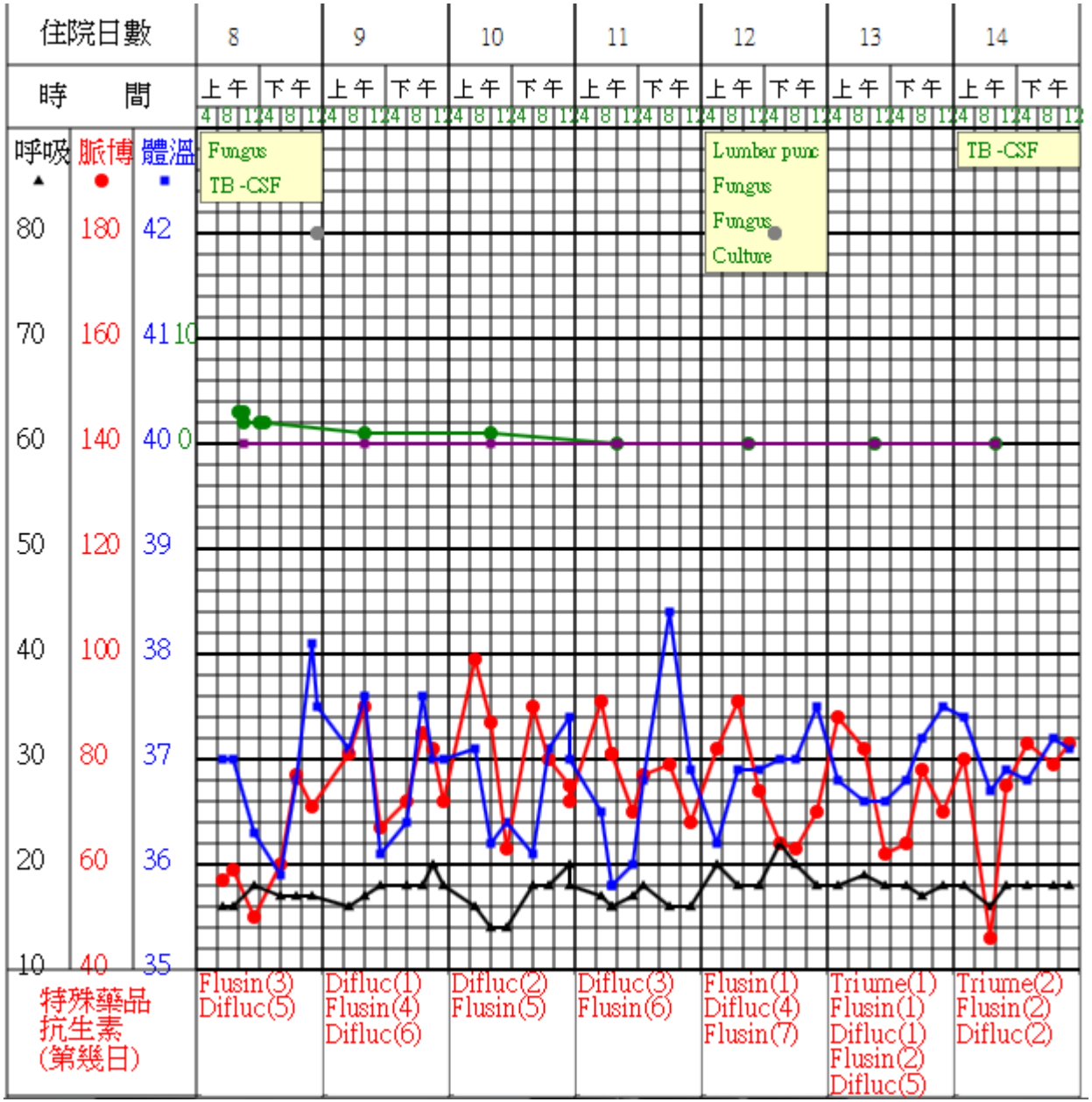
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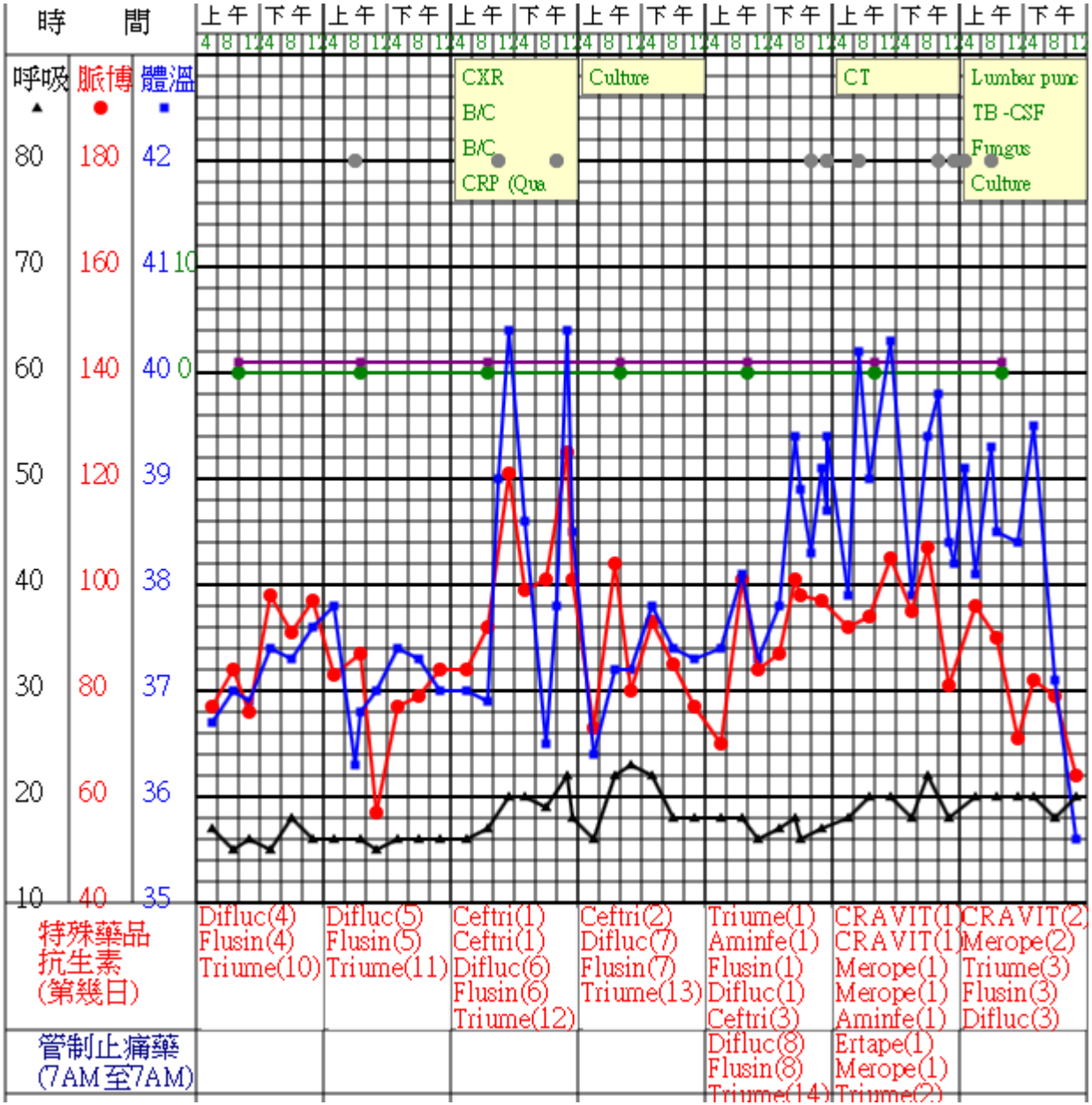
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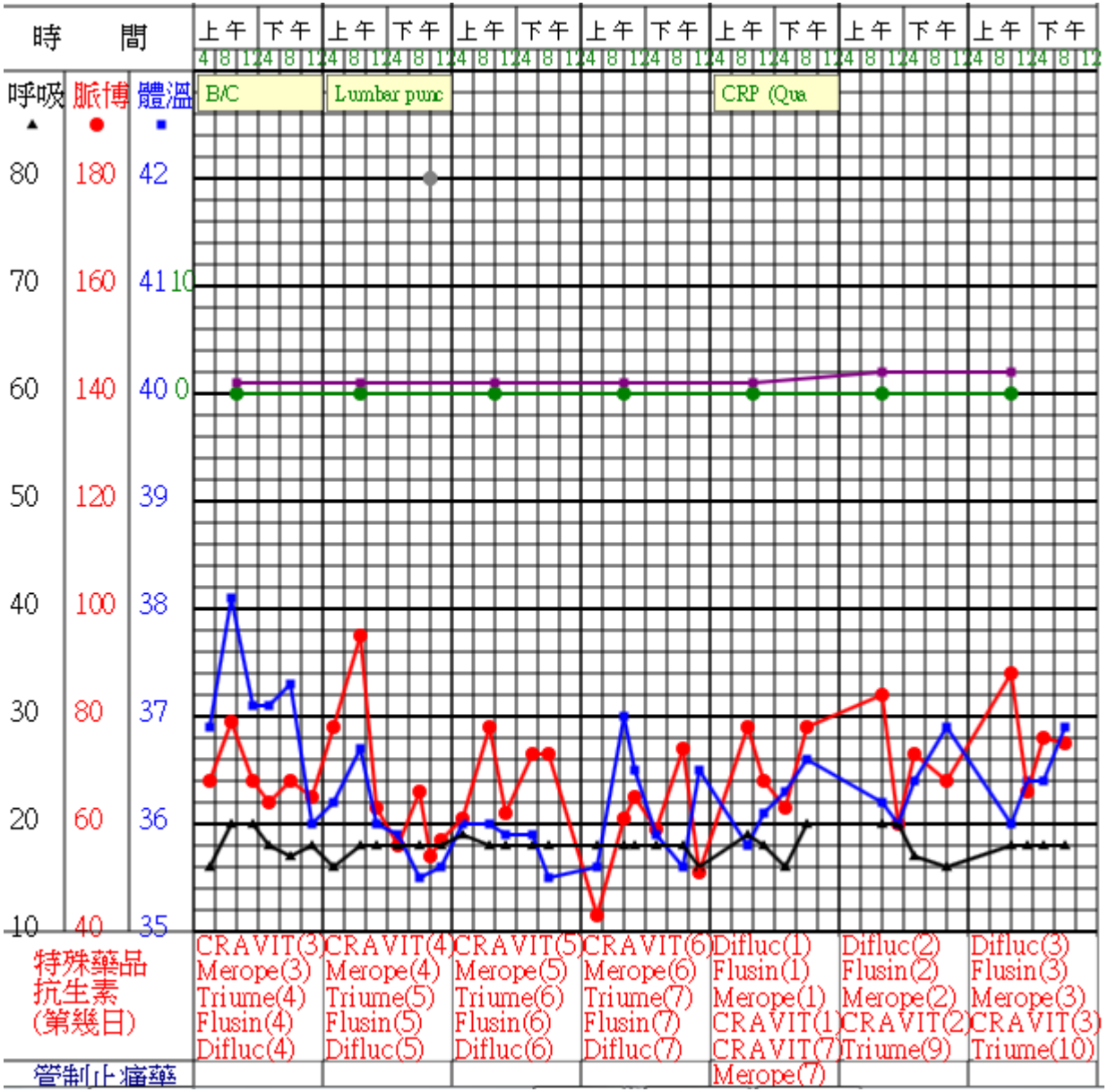
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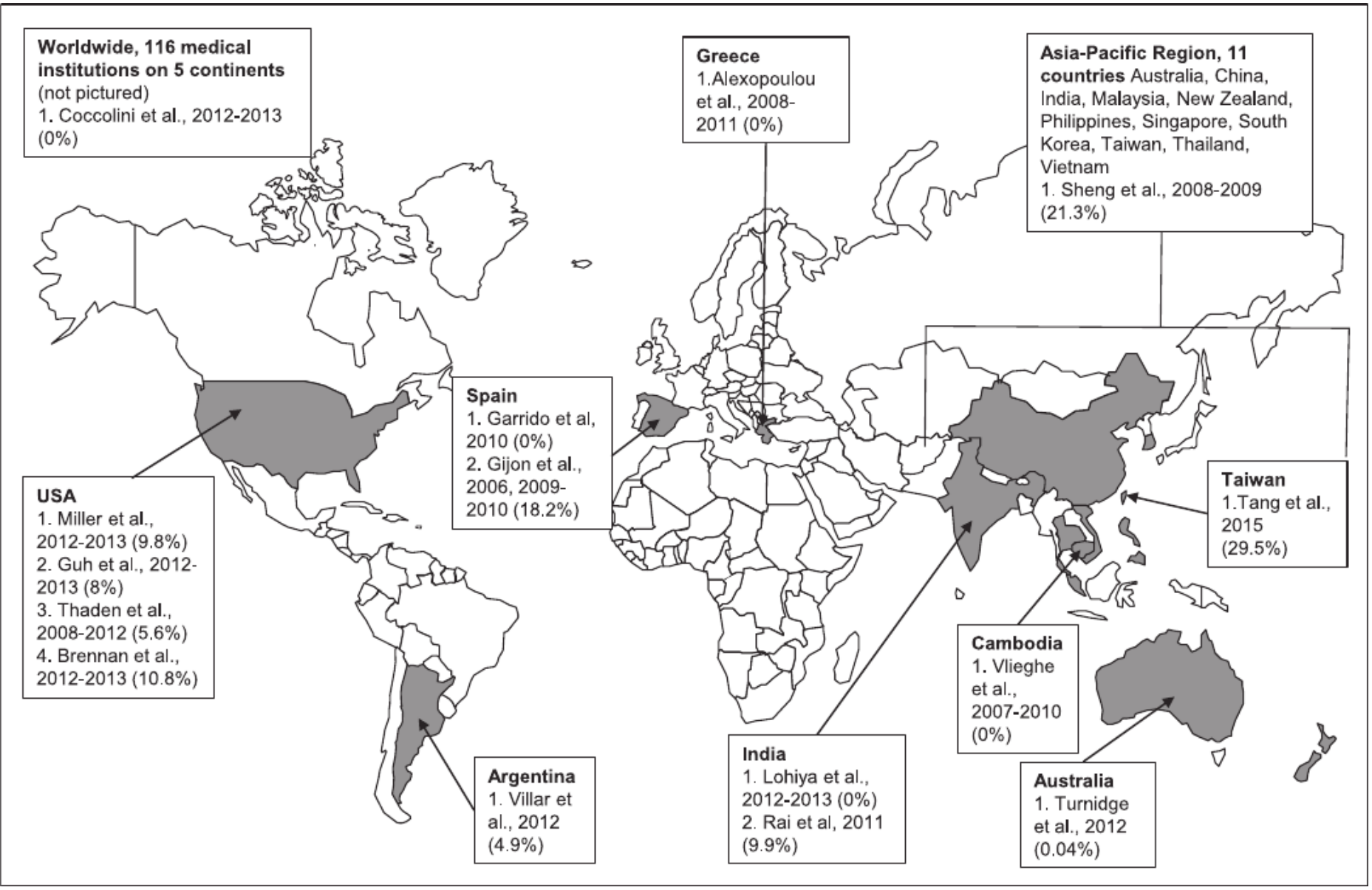
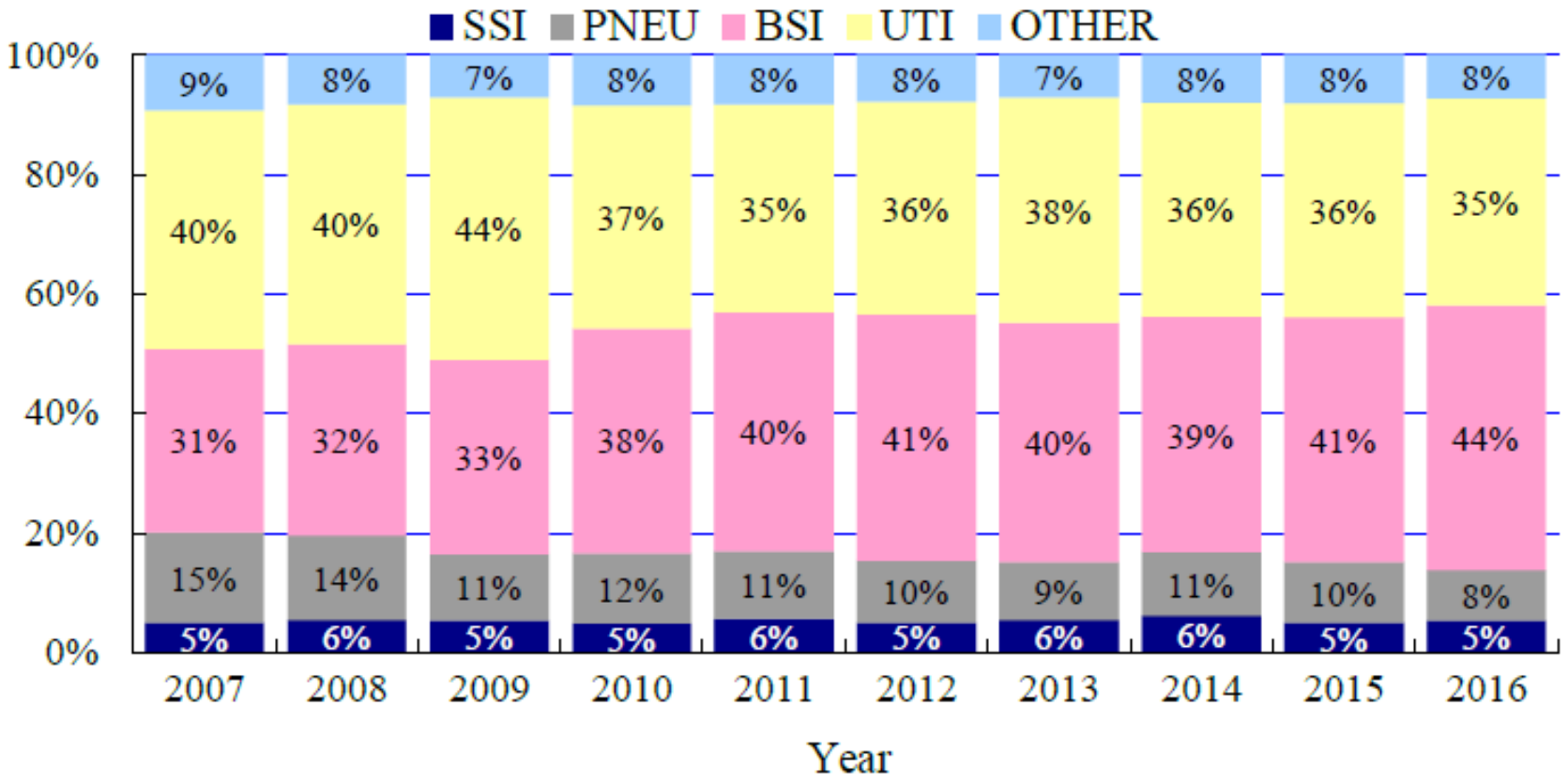
Difluc(3) Flusin(3) Merope(3) CRAVIT(3) Triume(10)
管制止痛藥

Geographical distribution of studies included in the review (percentage of community-associated or community-onset carbapenem-resistant Enterobacteriaceae).

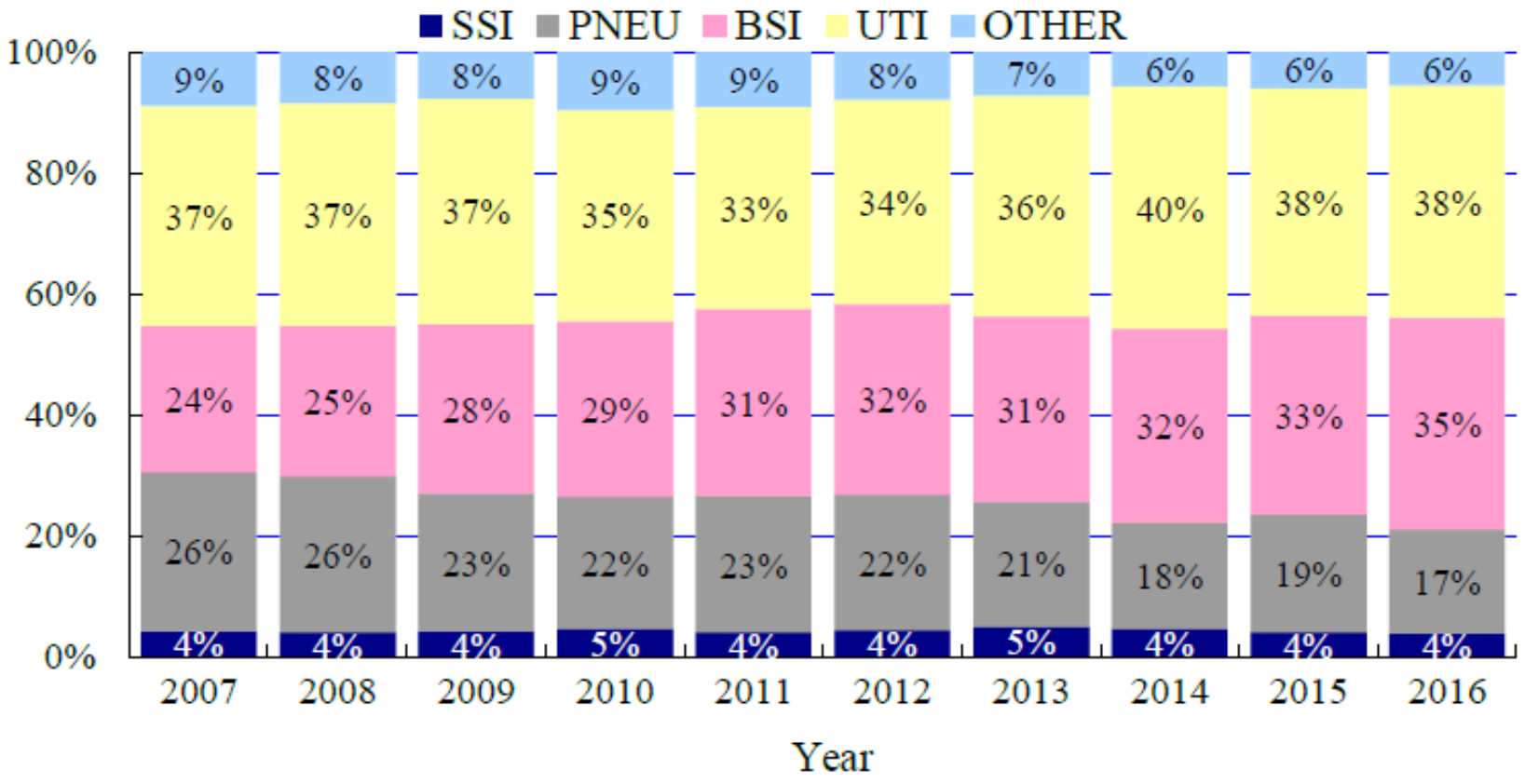


Int J Antimicrob Agents. 2017 Aug;50(2):127-134.

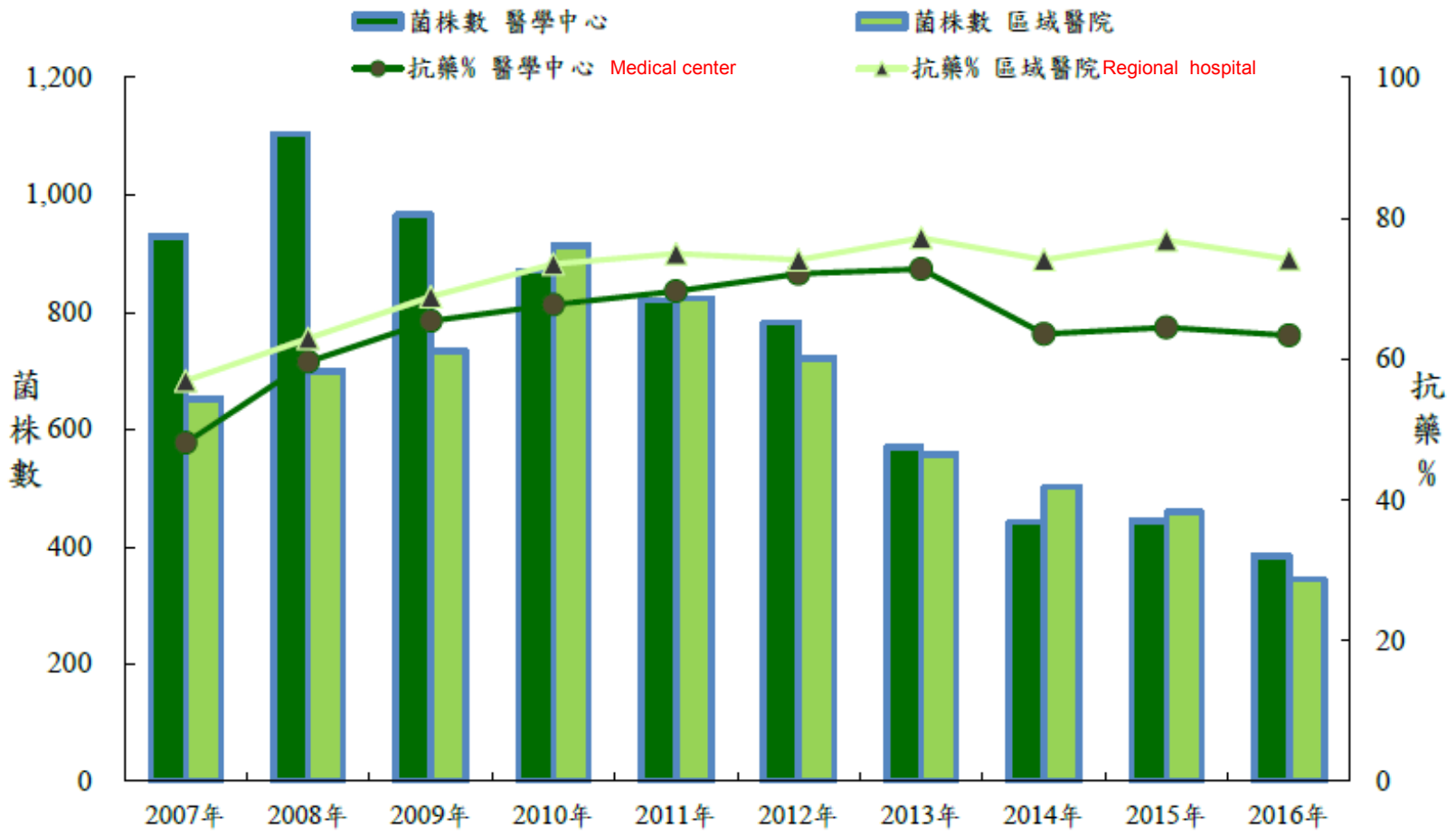
Health care associated infection, medical center ICU, 2007-2016
Taiwan Nosocomial Infections Surveillance System (TNIS)



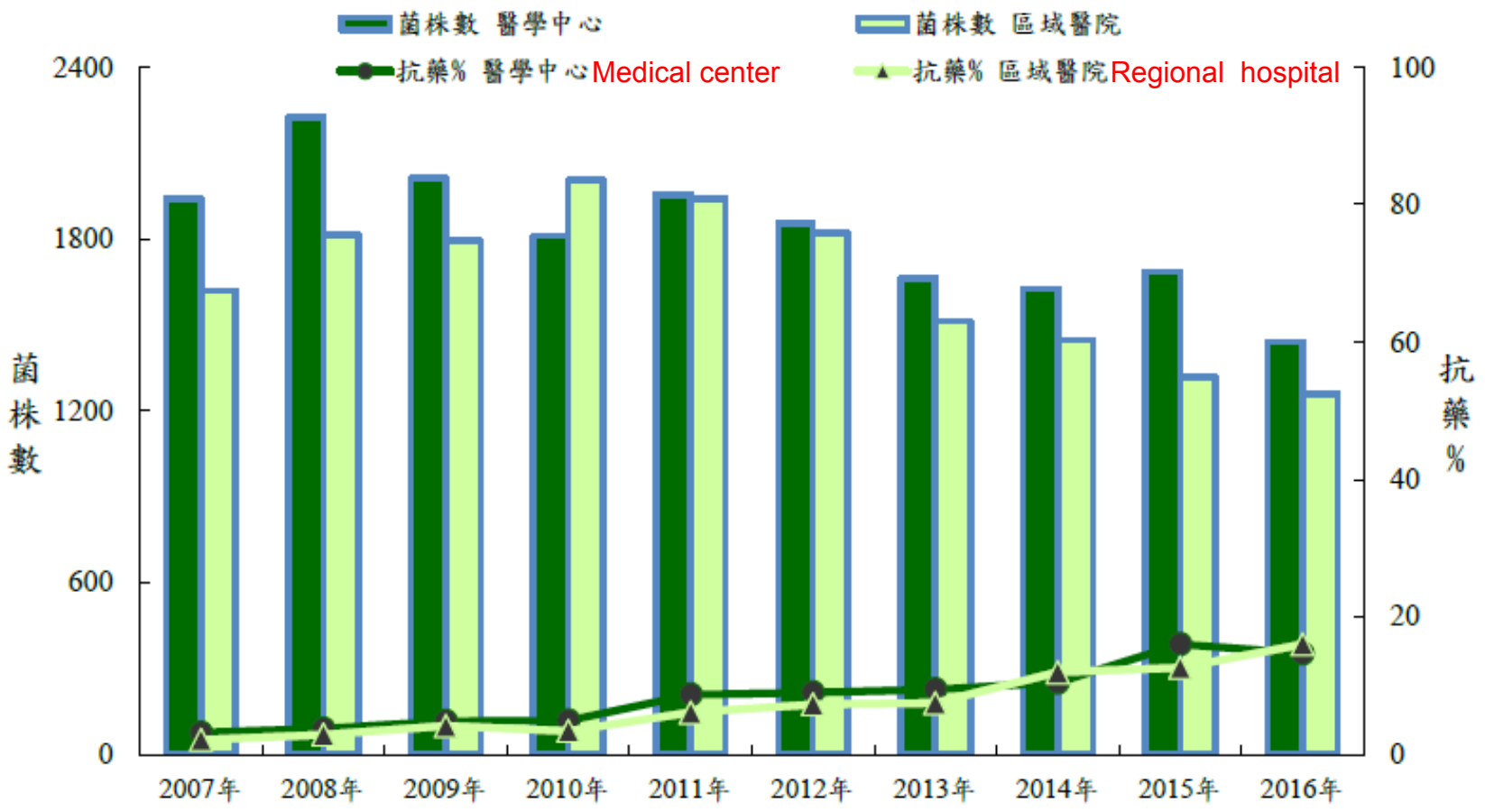
Health care associated infection, regional hospital ICU, 2007-2016
Taiwan Nosocomial Infections Surveillance System (TNIS)



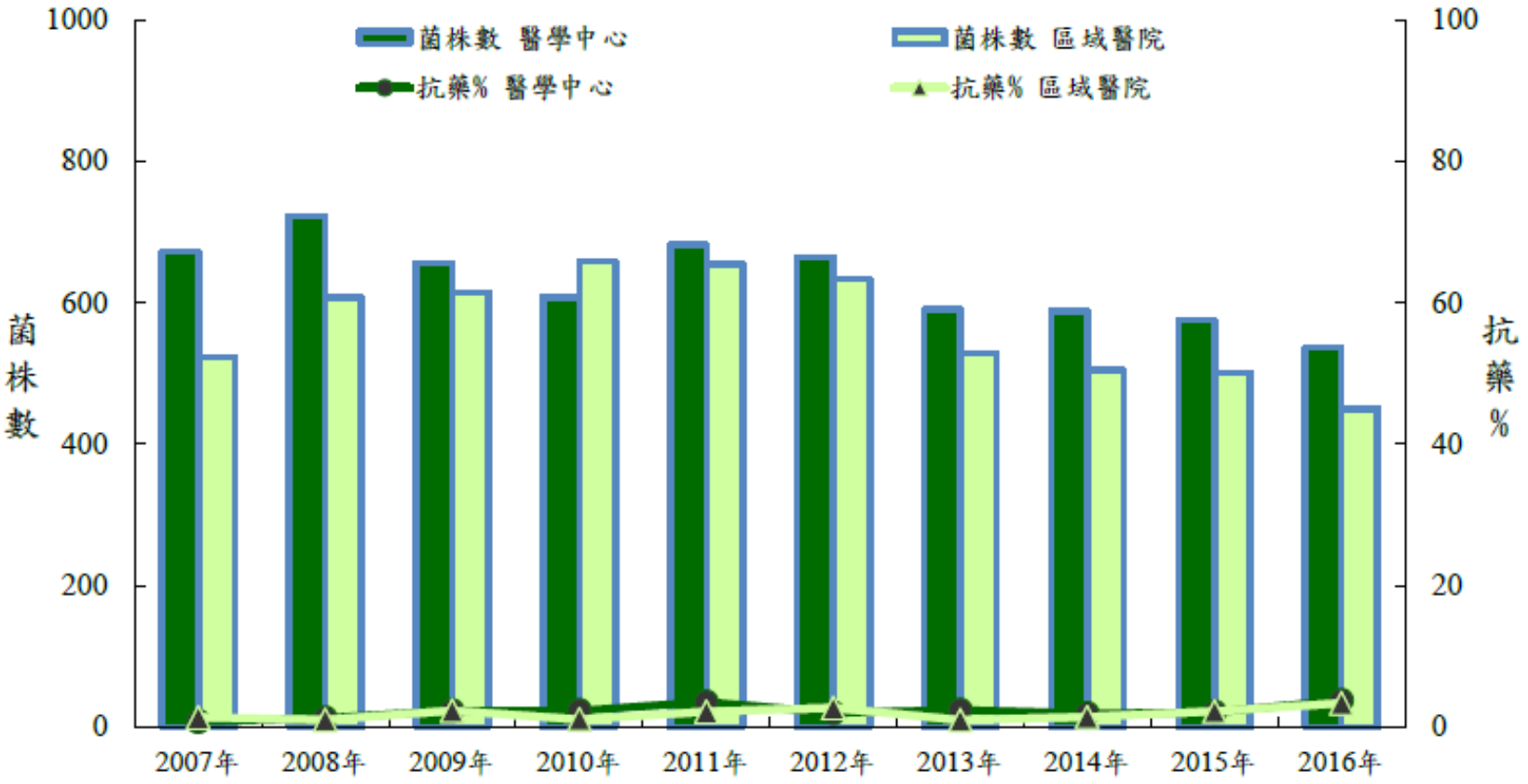
Health care associated infection in ICU, 2007-2016, TNIS
No of *A. baumanni* strains and % of carbapenem-resistant strains (CRAB)



Health care associated infections in ICU, 2007-2016, TNIS
No of *Enterobacteriaceae* and % of CRE

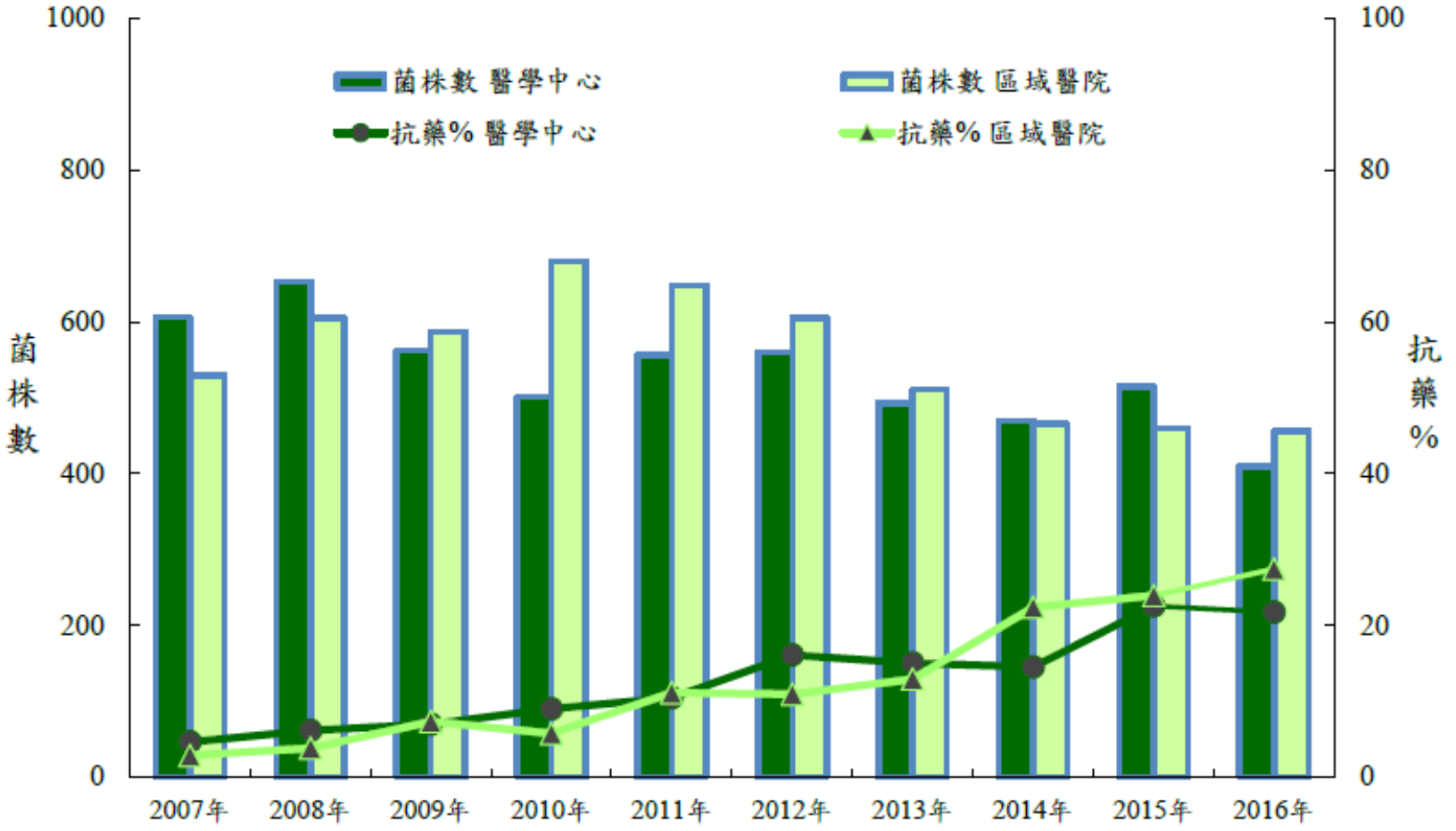


Health care associated infections in ICU, 2007-2016, TNIS
No of *E.Coli* and % of CR-*E. coli*



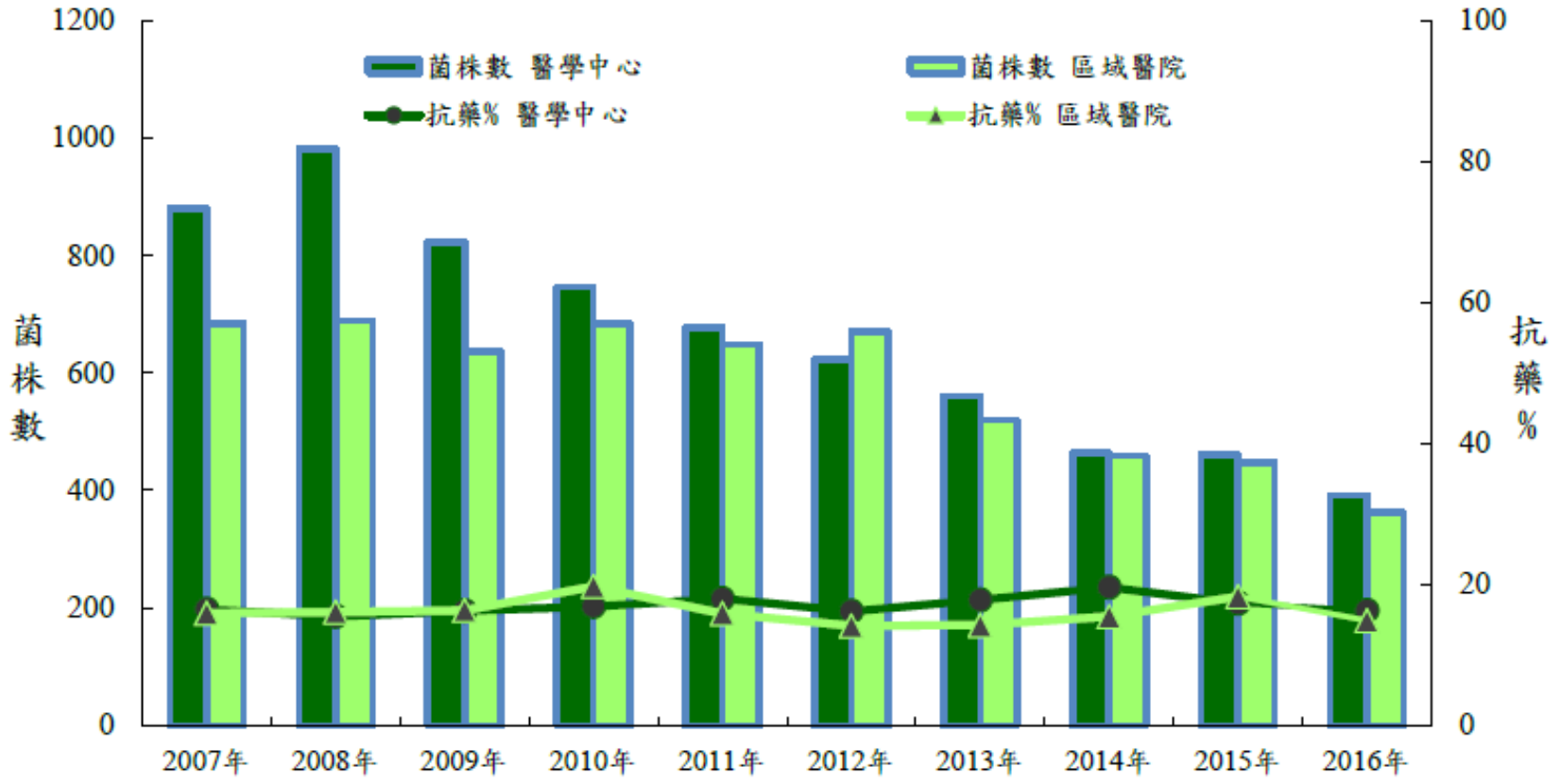
Health care associated infections in ICU, 2007-2016, TNIS

No of *K. Pneumoniae* and % of CR-*K. Pneumoniae*

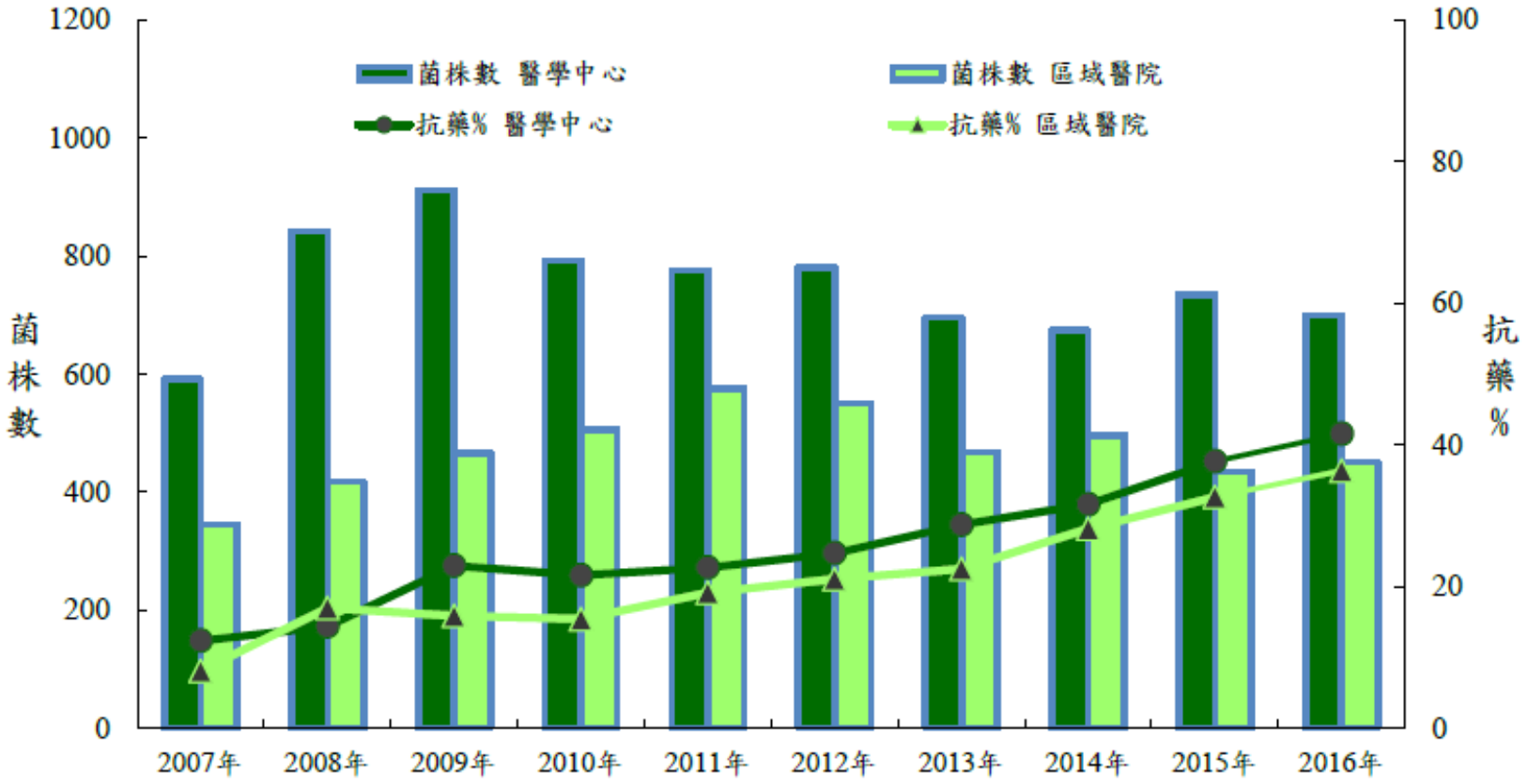


Health care associated infections in ICU, 2007-2016, TNIS

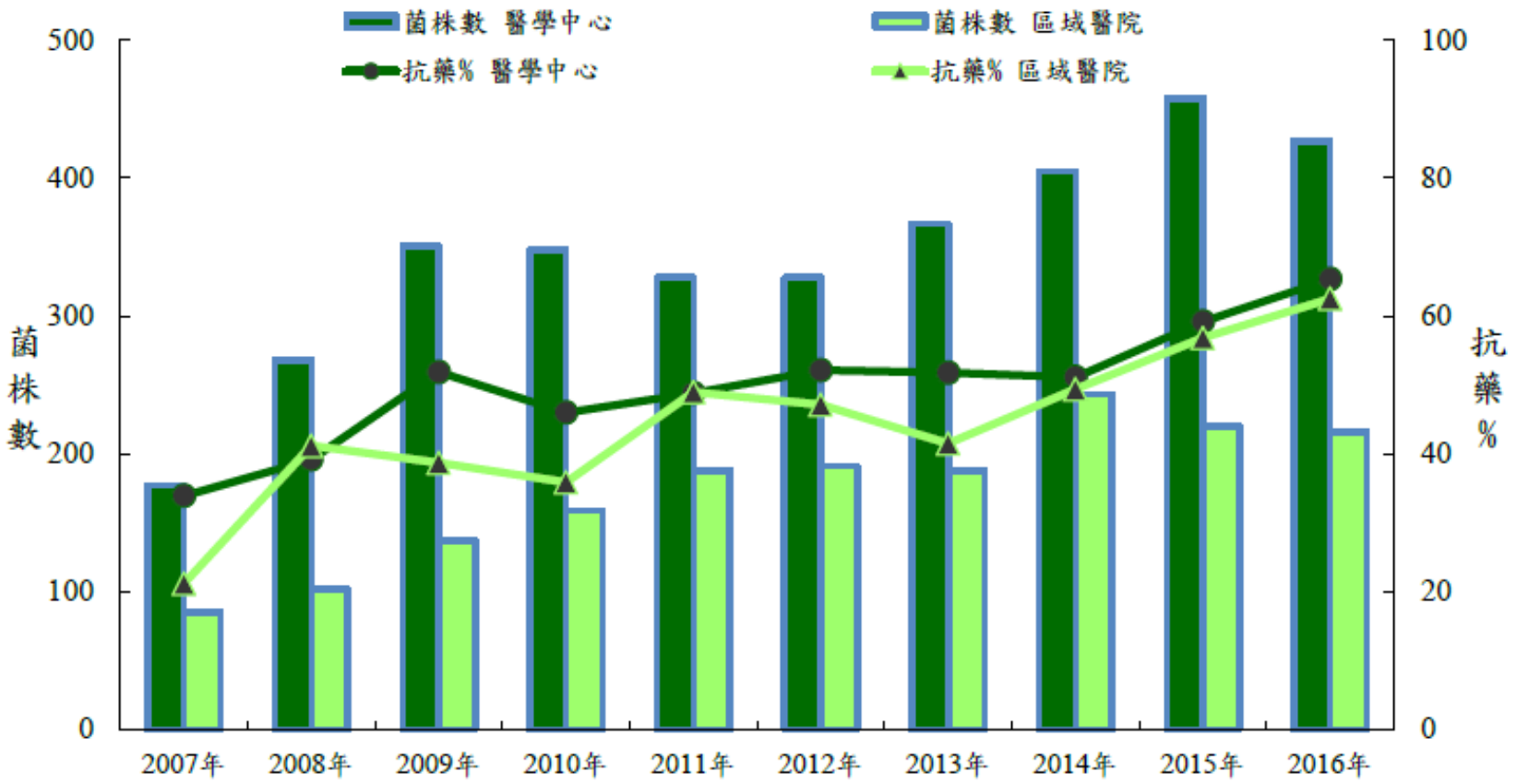
No of *P. aeruginosa* and % of CR- *P. aeruginosa*



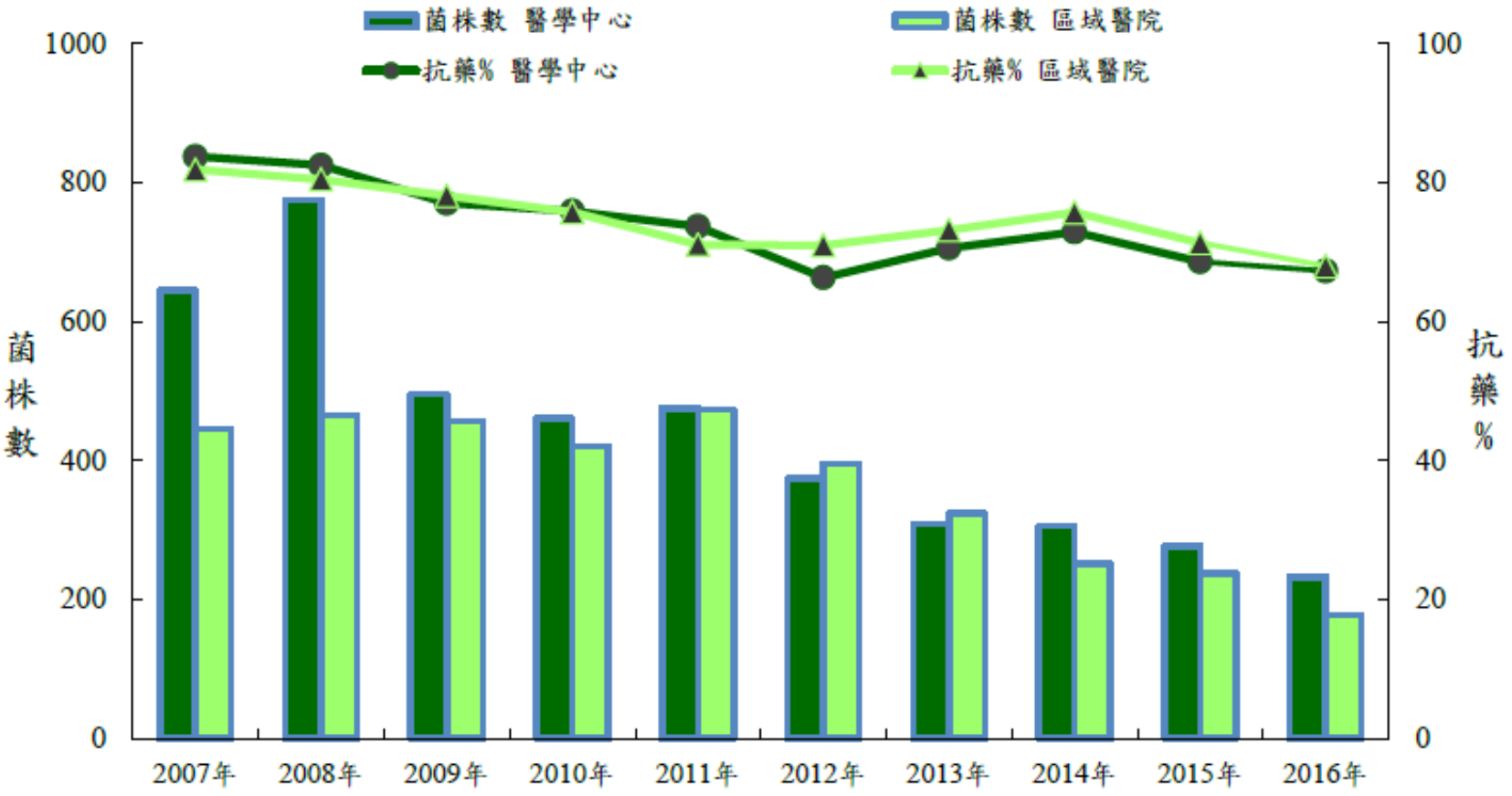
Health care associated infections in ICU, 2007-2016, TNIS
No of *Enterococcus* and % of VRE



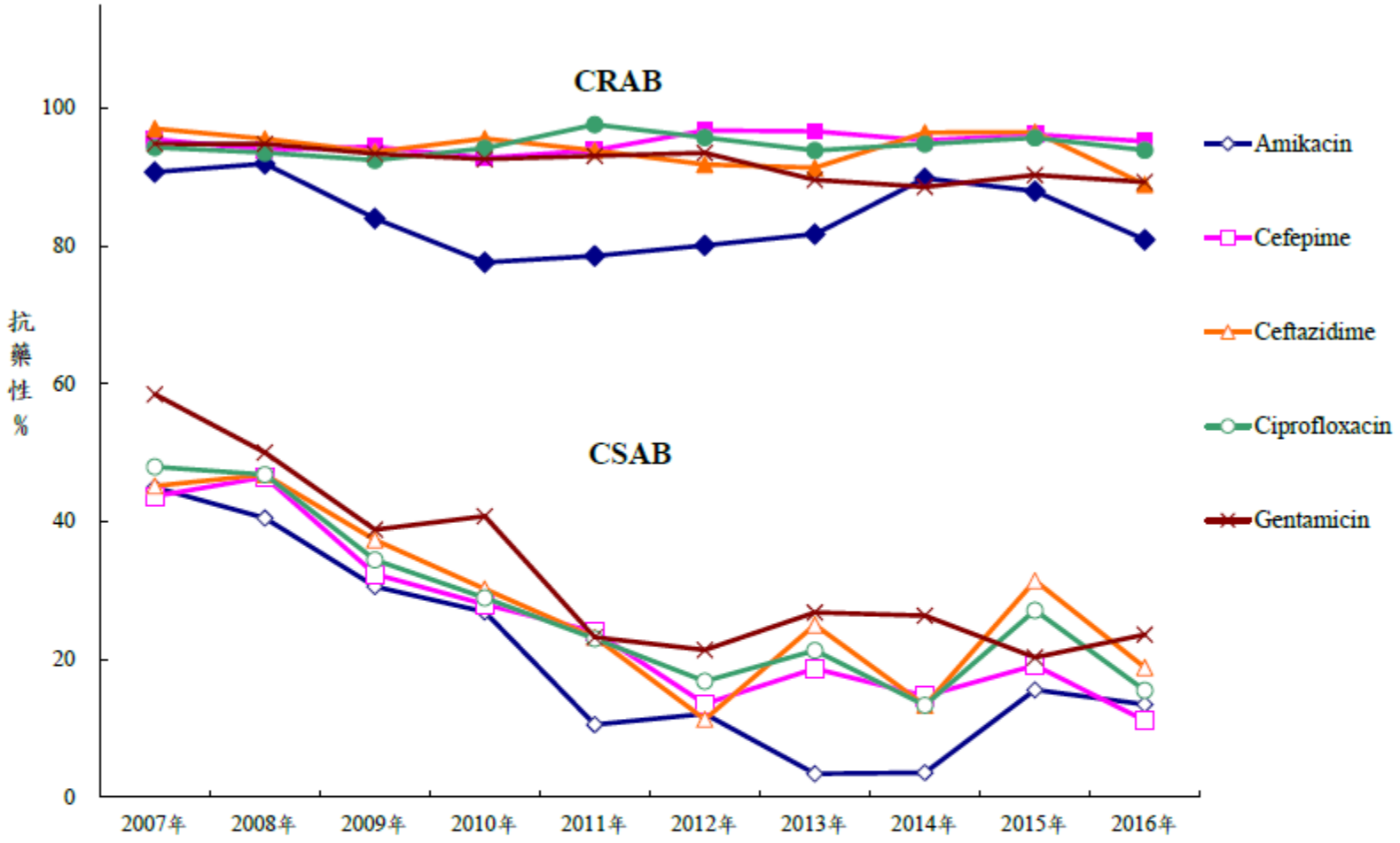
Health care associated infections in ICU, 2007-2016, TNIS
No of *E. faecium* and % of VRE. *faecium*



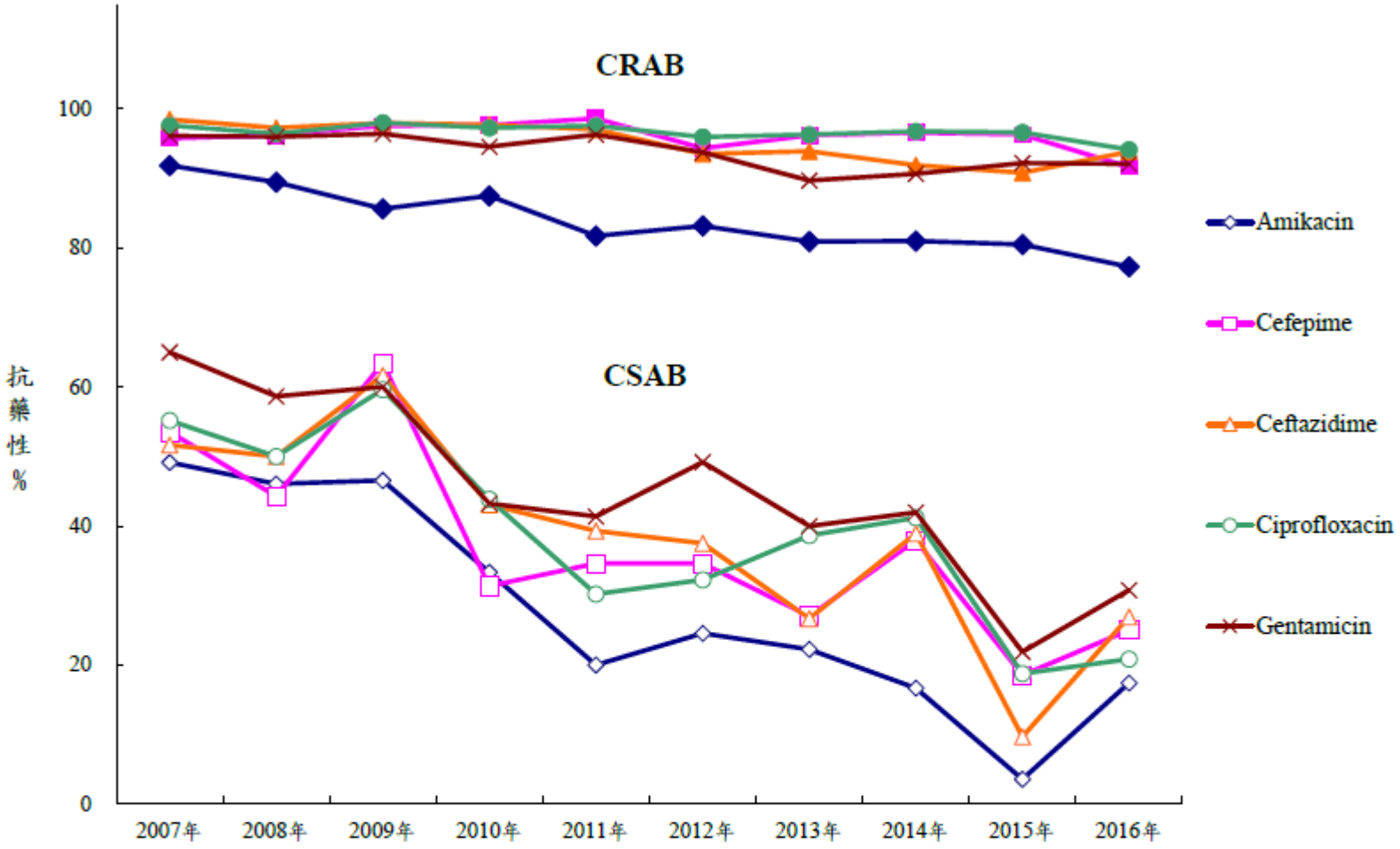
Health care associated infections in ICU, 2007-2016, TNIS
No of *S. aureus* and % of MRSA



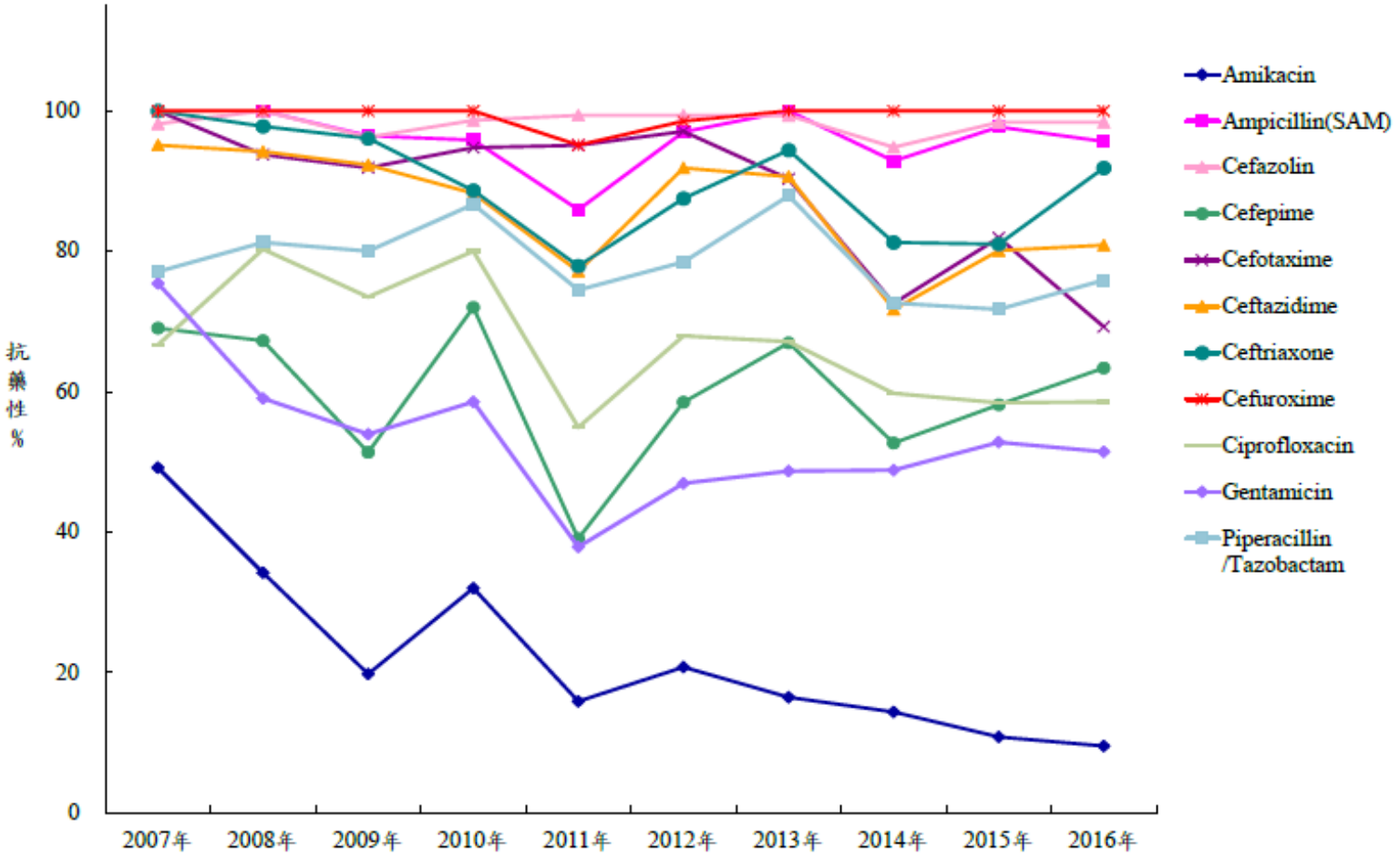
Health care associated infection, medical center ICU, 2007-2016, TNIS
% of *Acinetobacter baumannii* resistance



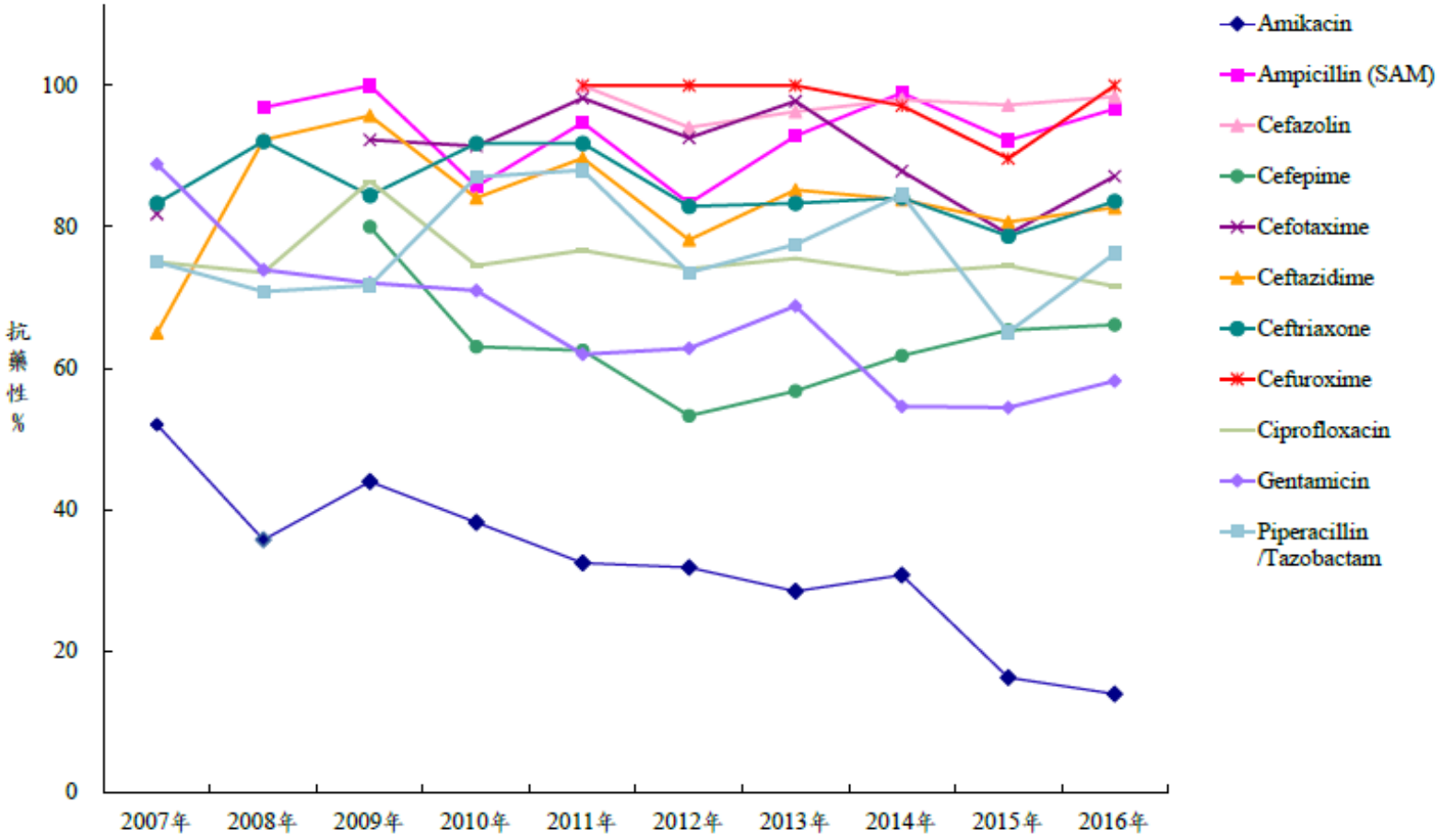
Health care associated infection, regional hospital ICU, 2007-2016, TNIS
% of *Acinetobacter baumannii* resistance



Health care associated infection, medical center ICU, 2007-2016, TNIS
% of CRE drug resistance



Health care associated infection, regional hospital ICU, 2007-2016, TNIS
% of CRE drug resistance



Health care associated infection, medical center ICU, 2007-2016, TNIS
Ranking of organisms

菌株	2007年 排名	2008年 排名	2009年 排名	2010年 排名	2011年 排名	2012年 排名	2013年 排名	2014年 排名	2015年 排名	2016年 排名
Escherichia coli	3	4	4	4	2	2	1	1	1	1
Enterococcus faecium	12	11	10	10	11	10	8	7	5	2
Klebsiella pneumoniae	4	6	5	5	5	5	5	3	3	3
Candida albicans	6	2	2	3	3	4	2	2	2	4
Pseudomonas aeruginosa	2	3	3	2	4	3	3	4	4	5
Acinetobacter baumannii	1	1	1	1	1	1	4	5	6	6
Yeast-like	7	7	6	6	7	6	6	6	7	7
Other *Candida* spp. or NOS	10	10	7	8	8	7	7	8	8	8
Enterobacter species	8	8	9	9	9	9	10	10	9	9
Enterococcus faecalis	11	12	12	13	13	13	11	11	11	10

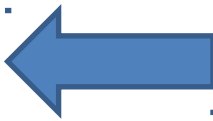
Health care associated infection, regional hospital ICU, 2007-2016, TNIS
Ranking of organisms

	2007年	2008年	2009年	2010年	2011年	2012年	2013年	2014年	2015年	2016年
菌株	排名	排名	排名	排名	排名	排名	排名	排名	排名	排名
Klebsiella pneumoniae	3	4	4	2	3	4	4	4	3	1
Escherichia coli	3	3	3	4	2	3	1	2	1	2
Candida albicans	6	5	5	5	5	5	5	1	2	3
Pseudomonas aeruginosa	1	2	2	3	4	2	3	5	5	4
Acinetobacter baumannii	2	1	1	1	1	1	2	3	4	5
Enterococcus faecium	14	14	12	11	11	10	10	7	7	6
Other *Candida* spp. or NOS	10	10	10	9	9	9	8	8	8	7
Staphylococcus aureus	5	6	6	6	6	6	6	6	6	8
Enterobacter species	7	7	7	8	8	8	7	9	9	9
Enterococcus faecalis	15	14	15	14	12	12	12	11	11	10

Table 1 Antimicrobial susceptibility testing results for carbapenem-non-susceptible *E. coli* isolates in 2010 and 2012

Antibiotics	ertapenem-non-susceptible *E. coli* (8 hospitals) and imipenem- or meropenem-non-susceptible *E. coli* (17 hospitals)							
	2010 (n = 32)				2012 (n = 43)			
	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Resistance (%)	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Resistance (%)
Ertapenem	2- ≥ 8	≥8	≥8	100	1- ≥ 8	≥8	≥8	100
Imipenem	1- ≥ 8	4	≥8	56.3	1- ≥ 8	≥8	≥8	72.1
Meropenem	0.12- ≥ 8	2	8	31.3	0.5- ≥ 8	4	≥8	58.1
Doripenem	0.12- ≥ 4	1	4	15.6	0.5- ≥ 4	≥4	≥4	51.2
Amikacin	≤4-64	4	32	6.3	≤4-32	≤4	16	0
Gentamicin	≤1- ≥ 16	2	≥16	40.6	≤1- ≥ 16	4	≥16	45.7
Cefazolin	≥32	≥32	≥32	100	≥32	≥32	≥32	100
Cefotaxime	4- ≥ 64	≥64	≥64	100	32- ≥ 64	≥64	≥64	100
Cefoxitin	≥32	≥32	≥32	100	≥32	≥32	≥32	100
Ceftazidime	16- ≥ 32	≥32	≥32	100	≥32	≥32	≥32	100
Cefepime	0.25- ≥ 32	8	≥32	18.8	2- ≥ 32	16	≥32	46.5
Ciprofloxacin	0.06- ≥ 4	≥4	≥4	75.0	≤0.06- ≥ 4	≥4	≥4	79.1
Tigecycline	≤0.25-1	≤0.25	0.5	0	≤0.25- ≥ 4	≤0.25	0.5	7.0
Colistin	≤0.5-2	1	2	0	≤0.5- ≥ 4	≤0.5	1	2.3
SXT[a]	0.06- ≥ 16	≥16	≥16	62.5	≤2/38- ≥ 4/76	≥4/76	≥4/76	76.7

[a]SXT: Trimethoprim/sulfamethoxazole. Trimethoprim/sulfamethoxazole MICs are presented according to the concentration of trimethoprim in 2010.



Ma et al. BMC Infectious Diseases 2013, 13:599

Table 1. Regional distributions of the participating hospitals, carbapenem non-susceptible *K. pneumoniae* isolates, and *K. pneumoniae* carbapenemase-2-producing *K. pneumoniae*.

Location	Number of participating hospitals		CRKP isolates		Serving population[a]	No. of KPC-2 isolates
	2010	2012	2010	2012		
North	4	6	67	206	~8,265,000	38
West	2	3	16	19	~5,766,000	1
South	2	5	17	20	~6,325,000	2
East	0	3	0	2	~1,024,000	0
Total	8	17	100	247	~21,380,000	41

[a]Population was presented according to the data of National Statics, ROC (Taiwan) in 2012.

doi:10.1371/journal.pone.0069428.t001

PLOS ONE July 2013, Volume 8, Issue 7

Table 2. Results of the antimicrobial susceptibility tests for carbapenem non-susceptible *K. pneumoniae* isolates collected in 2010 and 2012.

Antibiotics	2010 (N = 100 isolates)				2012 (N = 247 isolates)				p value
	MIC (mg/L)			Susceptibility [a]	MIC (mg/L)			Susceptibility[a]	
	Range	50	90	n (%)	Range	50	90	n (%)	
Ertapenem	1−≥8	≥8	≥8	0 (0.0)	≤0.25−≥8	≥8	≥8	2 (0.8)	1.000
Imipenem	0.5−≥8	≥8	≥8	4 (4.0)	0.5−≥8	≥8	≥8	3 (1.2)	0.109
Meropenem	≤0.25−≥8	≥8	≥8	8 (8.0)	≤0.25−≥8	≥8	≥8	66 (26.7)	<0.001
Doripenem	0.25−≥4	≥4	≥4	15 (15.0)	≤0.12−≥4	≥4	≥4	63 (25.5)	0.034
Amikacin	≤4−≥32	≥32	≥32	22 (22.0)	≤4−≥32	≤4	≥32	163 (66.0)	<0.001
Gentamicin	≤1−≥16	≥16	≥16	11 (11.0)	≤1−≥16	≥16	≥16	109 (44.1)	<0.001
Cefazolin	≥32	≥32	≥32	0 (0.0)	≥32	≥32	≥32	0(0.0)	NA
Cefotaxime	≤1−≥64	≥64	≥64	1 (1.0)	≥64	≥64	≥64	0 (0.0)	0.288
Cefoxitin	≥32	≥32	≥32	0 (0.0)	≥32	≥32	≥32	0 (0.0)	NA
Ceftazidime	4−≥32	≥32	≥32	1 (1.0)	≥32	≥32	≥32	0 (0.0)	0.288
Cefepime	≤1−≥32	≥32	≥32	6 (6.0)	≤1−≥32	≥32	≥32	27 (10.9)	0.156
Ciprofloxacin	0.25−≥4	≥4	≥4	7 (7.0)	≤0.06−≥4	≥4	≥4	21 (8.5)	0.642
Tigecycline	≤0.25−16	1	2	91 (91.0)	≤0.25−16	0.5	2	227 (91.9)	0.783
Colistin	1−≥4	2	≥4	83 (83.0)	≤0.5−≥4	≤0.5	≥4	217 (87.9)	0.231
SXT[b]	≤0.5−≥16	≥16	≥16	10 (10.0)	≤0.5−≥16	≥16	≥16	46 (18.6)	0.048

[a]Susceptibility was interpreted by using the CLSI 2012 criteria.
[b]Trimethoprim/sulfamethoxazole and MIC was presented according to the concentration of trimethoprim.
doi:10.1371/journal.pone.0069428.t002

Table 1. β-Lactamases carried by carbapenem-resistant *K. pneumoniae*, *E. coli* and *E. cloacae* isolates

β-Lactamases carried	*K. pneumoniae* (*n*=100)	*E. coli* (*n*=53)	*E. cloacae* (*n*=41)
None	0	2	14
One β-lactamase			
DHA-1	0	2	0
CMY-2	0	9	0
TEM-1	0	1	6
SHV-11	1	0	0
CTX-M-15	0	1	0
CTX-M-55	0	3	0
Two β-lactamases			
DHA-1, TEM-1	0	0	1
DHA-1, SHV-1	1	0	0
DHA-1, SHV-11	1	0	0
DHA-1, SHV-28	1	0	0
CMY-2, TEM-1	0	17	0
CMY-2, SHV-31	1	0	0
CMY-2, CTX-M-15	0	2	0
CMY-2, CTX-M-27	0	1	0
TEM-1, SHV-12	0	0	14
TEM-1, CTX-M-15	0	0	1
TEM-176, CTX-M-55	0	1	0
SHV-12, CTX-M-14	1	0	0
SHV-12, IMP-8	0	0	4
SHV-155, KPC-2	1	0	0
Three β-lactamases			
DHA-1, TEM-1, SHV-1	1	0	0
DHA-1, TEM-1, SHV-5	1	0	0
DHA-1, TEM-1, SHV-11	3	0	0
DHA-1, TEM-1, CTX-M-14	1	0	0
DHA-1, SHV-11, CTX-M-14	3	0	0
CMY-2, TEM-1, SHV-11	1	0	0
CMY-2, TEM-1, CTX-M-14	0	8	0
CMY-2, TEM-1, CTX-M-55	0	3	0
TEM-1, SHV-11, CTX-M-14	8	0	0
TEM-1, SHV-12, CTX-M-14	1	0	0
TEM-1, SHV-12, IMP-8	0	0	1
TEM-1, CTX-M-14, CTX-M-55	0	1	0
Four β-lactamases			
DHA-1, CMY-2, TEM-1, CTX-M-14	0	1	0
DHA-1, TEM-1, SHV-11, CTX-M-14	67	0	0
DHA-1, TEM-1, SHV-12, CTX-M-14	1	0	0
DHA-1, TEM-1, SHV-129, CTX-M-14	1	0	0
DHA-1, TEM-1, SHV-141, CTX-M-14	1	0	0
CMY-2, TEM-1, SHV-12, CTX-M-14	0	1	0
TEM-1, SHV-31, CTX-M-14, KPC-2	1	0	0
Five β-lactamases			
DHA-1, TEM-1, SHV-11, CTX-M-14, IMP-8	1	0	0
DHA-1, TEM-1, SHV-11, CTX-M-14, CTX-M-3	1	0	0
DHA-1, CMY-2, TEM-1, SHV-11, CTX-M-14	1	0	0

J Antimicrob Chemother 2014
doi:10.1093/jac/dku204

CDC Surveillance definition for CRE

- In January 2015, The Centers for Disease Control and Prevention (CDC) modified its surveillance definition for CRE to the current definition (resistant to imipenem, meropenem, doripenem, or ertapenem OR documentation that the isolate possess a carbapenemase).

Carbapenem-Nonsusceptible Enterobacteriaceae in Taiwan

- 1135 carbapenem-resistant (nonsusceptible) Enterobacteriaceae (CRE) isolates were recovered between November 2010 and July 2012 (517 from 2010-2011 and 618 from 2012) from 4 hospitals in Taiwan.
- Carbapenemase-producing Enterobacteriaceae (CPE) comprised 5.0% (57 isolates), including 17 KPC-2, 1 NDM-1 and 37 IMP-8 and 2 VIM-1
- 518 CRE isolates (45.6%) were positive for blaESBL, while 704 (62.0%) isolates were blaAmpC-positive, 382 (33.6% overall) of which carried both blaESBL and blaAmpC. CTX-M(414, 80.0%) was the most common blaESBL, while DHA (497, 70.6%) and CMY (157, 22.3%) were the most common blaAmpC.
- Co-carriage of blaESBL and blaAmpC was detected in 31 (54.4%) and 15 (26.3%) of the 57 CPE, respectively

Wang J-T, Wu U-I, Lauderdale T-LY, Chen M-C, Li S-Y, Hsu L-Y, et al. (2015) Carbapenem-Nonsusceptible Enterobacteriaceae in Taiwan. PLoS ONE 10(3): e0121668.

Table 3. ESBL, AmpC β-lactamases, and carbapenemase genes detected in carbapenem-non-susceptible Enterobacteriaceae.

Species (no. of tested)	Gene type and no. of isolates positive		Combination of bla_{ESBL} / bla_{AmpC} (n, %)				
	bla_{ESBL}	bla_{AmpC}	+ / -	- / +	+ / +	- / -	Major combination
K. pneumoniae (577)	CTX-M (291), SHV (56), CTX-M+SHV (37)	DHA (458), CMY (17),CMY + DHA (12), MIR (2)	64 (11.1)	169 (29.2)	320 (55.4)	24 (4.2)	CTX-M & DHA (85.6%, 274/320)[a]
E. cloacae (267)	SHV (43), CTX-M + SHV (3), CTX-M (2)	MIR (34), ACT (25), DHA (9), CMY (2), DHA+MIR (1), DHA +CMY (1)	39 (14.6)	63 (23.6)	9 (3.4)	156 (58.4)	SHV & ACT (77.8%, 7/9)
E. coli (145)	CTX-M (66), CTX-M+SHV (1)	CMY (109), DHA (6), ACT (1)	20 (13.8)	69 (47.6)	47 (32.4)	9 (6.2)	CTX-M & CMY (93.6%, 44/47)
E. aerogenes (88)	CTX-M (2), SHV (1)	DHA (2)	3 (3.4)	2 (2.3)	0	83 (94.3)	-
C. freundii (20)	CTX-M (2), SHV (2), both (1)	CMY (10), DHA (1)	0	6 (30.0)	5 (25.0)	9 (45.0)	SHV & CMY (2)
S. marcescens (14)	CTX-M (2), SHV (1)	DHA (2)	3 (21.4)	2 (14.3)	0	9 (64.3)	-
M. morgannii (5)	0	DHA (5)	0	5 (100)	0	0	
P. stuartii (5)	CTX-M (1)	CMY (2), DHA(1)	1 (20)	3 (60)	0	1 (20)	
C. diversus (3)	CTX-M (1), CTX-M+SHV (1)	CMY (2)	1 (33.3)	1 (33.3)	1 (33.3)	0	CTX-M & CMY (1)
K. oxytoca (2)	CTX-M+SHV (1), SHV +OXY-5 (1)	0	2 (100)	0	0	0	-
P. rettgeri (3)	CTX-M (1)	CMY (1)	1 (33.3)	1 (33.3)	0	1 (33.3)	-
R. planticola (4)	0	0	0	0	0	4 (100)	-
C. koseri (2)	CTX-M (1)	CMY (1)	1 (50)	1 (50)	0	0	
ALL	CTX-M (369), CTX-M+SHV (45), SHV (103), SHV +OXY-5 (1)	DHA (484), CMY (144), MIR (36), ACT (26), CMY+DHA (13), DHA+MIR (1)	135 (11.9)	322 (28.4)	382 (33.7)	296 (26.1)	CTX-M+DHA (254), CTX-M +CMY (49), SHV+DHA(45)

[a] % is no. of isolates with the combination/no. of isolates positive for both bla_{ESBL} and bla_{AmpC}.

doi:10.1371/journal.pone.0121668.t003

Wang JT, Wu UI, Lauderdale TLY, Chen MC, Li SY, et al. (2015) Carbapenem-Nonsusceptible Enterobacteriaceae in Taiwan. PLOS ONE 10(3): e0121668. https://doi.org/10.1371/journal.pone.0121668
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0121668

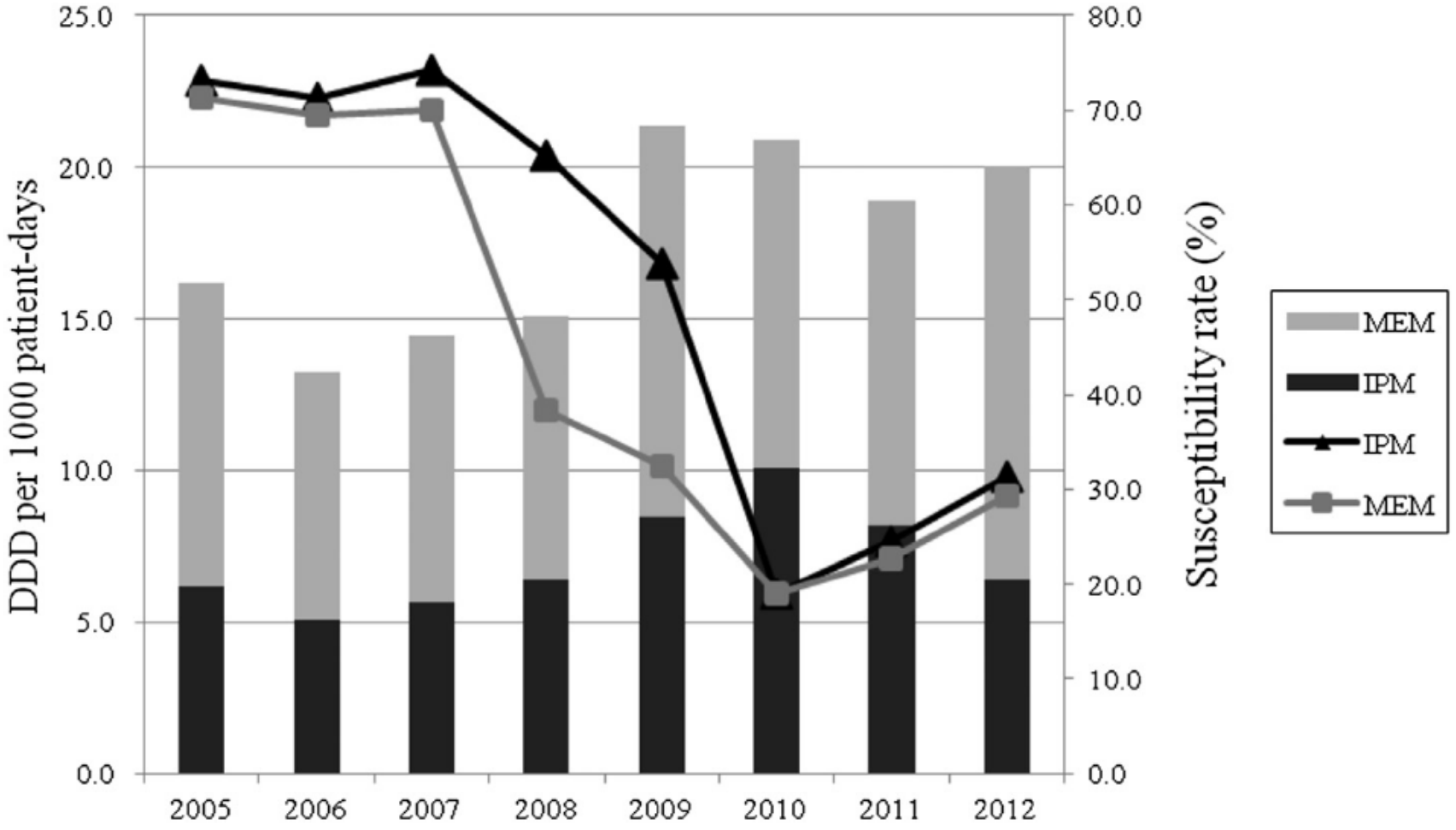


Figure 4. Susceptibility of *Acinetobacter baumannii* to imipenem and meropenem (curves) and and carbapenem use, depicted as the defined daily dose per 1000 patient-days (bars) from 2005 to 2012. DDD =defined daily dose; IPM = imipenem; MEM = meropenem.

Journal of Microbiology, Immunology and Infection (2015) 48, 57-64

Figure 1. Broad-spectrum antibiotic consumption in defined daily doses/1000 patient-days at each hospital. (A) Piperacillin/tazobactam. (B) Fluoroquinolones. (C) Class 2 carbapenems. (D) Extended-spectrum cephalosporins. (E) Total.

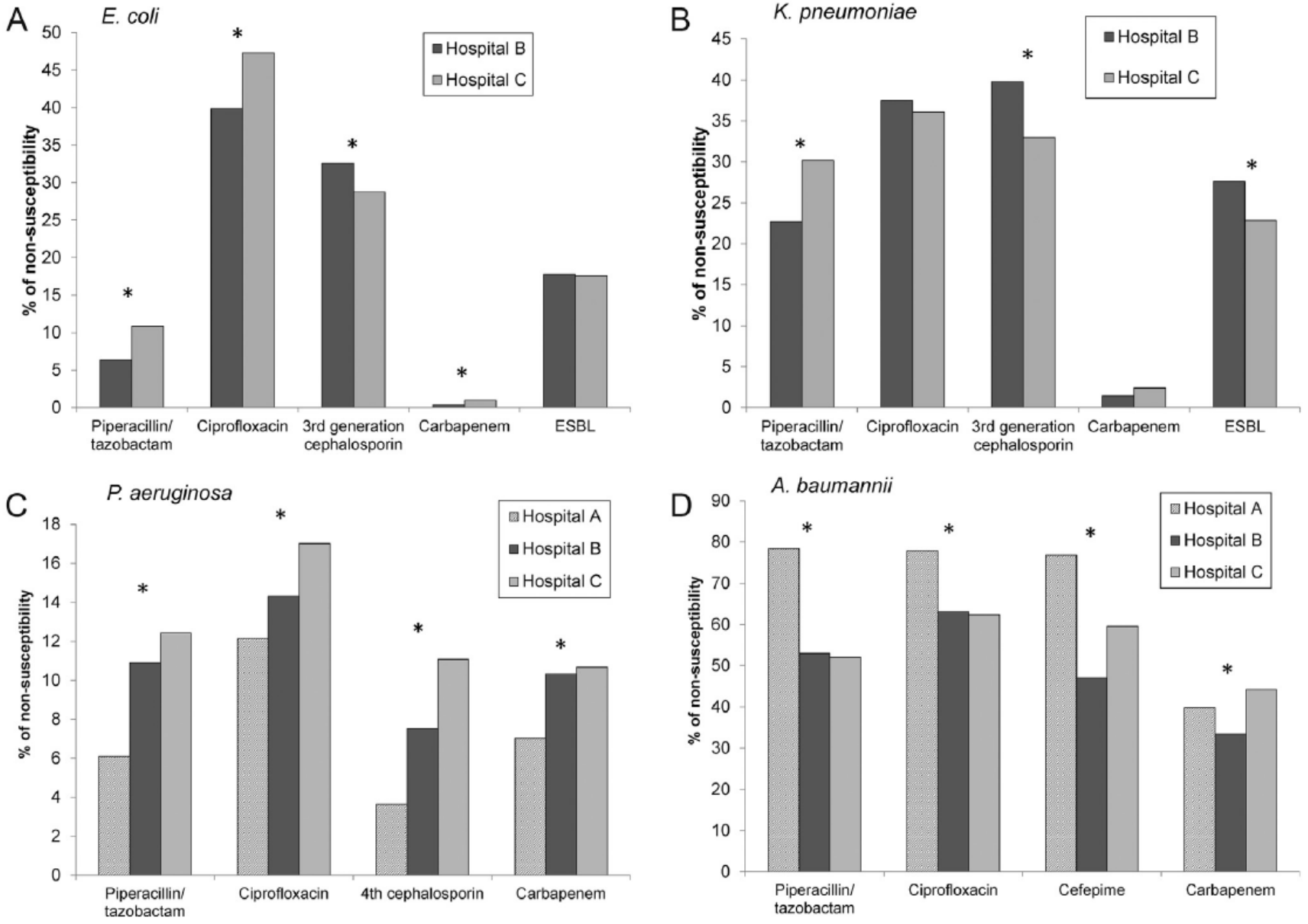


Figure 2. Comparison of non-susceptibility among (A) *Escherichia coli*, (B) *Klebsiella pneumoniae*, (C) *Pseudomonas aeruginosa*, and (D) *Acinetobacter baumannii* at three medical centers. An asterisk indicates that the nonsusceptibility rate is significantly different ($p \leq 0.05$).

Table 3 Multivariate analysis of risk factors for 30-day mortality among 46 patients infected with nonsusceptible *Klebsiella pneumoniae* and *Escherichia coli* in intensive care units

Variable	OR (95% CI)	*p*
Presentation with septic shock	12.14 (1.13–129.91)	0.04
Appropriate therapy at any time and for at least 48 h	0.22 (0.03–1.65)	0.14
APACHE II score	1.06 (0.94–1.19)	0.35
Diabetes mellitus	1.09 (0.21–5.68)	0.92

APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; OR = odds ratio.

Journal of Microbiology, Immunology and Infection (2015) 48, 219-225

Table 4 Detailed antimicrobial therapy of 42 patients infected with carbapenem nonsusceptible *Klebsiella pneumoniae* and/or *Escherichia coli* in the intensive care units

Antimicrobial regimens	*n* (%)	Mortality, *n* (%)
Appropriate antimicrobial therapy	33 (78.6)	12 (36.3)
Combination therapy	10 (23.8)	5 (50.0)
Tigecycline + colistin	5 (11.9)	2 (40.0)
Tigecycline + amikacin	2 (4.8)	1 (50.0)
Tigecycline + colistin + amikacin	2 (4.8)	1 (50.0)
Colistin + amikacin	1 (2.4)	1 (100.0)
Monotherapy	23 (54.8)	7 (30.4)
Tigecycline	10 (23.8)	2 (20.0)
Carbapenem[a]	6 (14.3)	2 (33.3)
Colistin	3 (7.1)	1 (33.3)
Fluoroquinolone[b]	2 (4.8)	1 (50.0)
Aminoglycoside[c]	2 (4.8)	1 (50.0)
Inappropriate antimicrobial therapy	9 (21.4)	7 (77.8)

[a] Two imipenem, three meropenem, one ertapenem.
[b] One levofloxacin, one ciprofloxacin.
[c] One gentamicin, one amikacin.

Journal of Microbiology, Immunology and Infection (2015) 48, 219-225

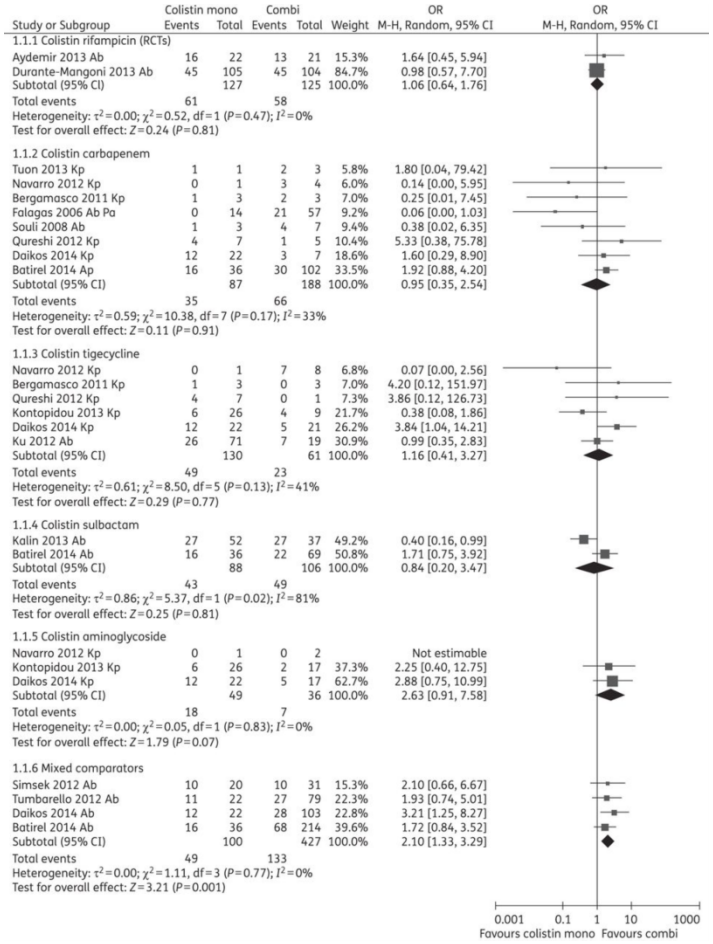
Table 1

Beta-lactamases that confer a carbapenem-resistance phenotype, their classification, common genetic platform and distribution among *Enterobacteriaceae*.

Enzyme/Ambler classification	Common genetic platform	Species distribution in *Enterobacteriaceae*
KPC (*Klebsiella pneumoniae* carbapenemase)/class A	*K. pneumoniae* sequence type 258 and ST11 inter alia, transposon Tn4401x	*Klebsiella pneumoniae, Escherichia coli, Enterobacter* sp.; diverse *Enterobacteriaceae*
NDM (New Delhi metallo-beta-lactamase)/class B	Various plasmid types	*K. pneumoniae* and *E. coli* predominantly; diverse *Enterobacteriaceae*
OXA-48 (oxacillinase)/class D	IncI/M-type plasmid	*K. pneumoniae* predominantly, diverse *Enterobacteriaceae*
VIM (Verona integron-encoded metallo-beta-lactamase)/class B	Gene cassettes in class 1 integrons	*K. pneumoniae*
IMP/class B	Gene cassettes in class 1 integrons	*K. pneumoniae*
SME/class A	Chromosome	*Serratia marcescens*
DHA-1/class C, in combination with OmpK35/36 loss	Plasmid	*K. pneumoniae*
ACT/class C, in combination with OmpK35/36 loss	Plasmid	*K. pneumoniae*
CTX-M-15/class A, in combination with OmpK35/36 loss	Plasmid	*K. pneumoniae*
SHV-5/class A, in combination with OmpK35/36 loss	Plasmid	*K. pneumoniae*
GES-5/class A, in combination with OmpK35/36 loss	Self-conjugative plasmid	*K. pneumoniae*

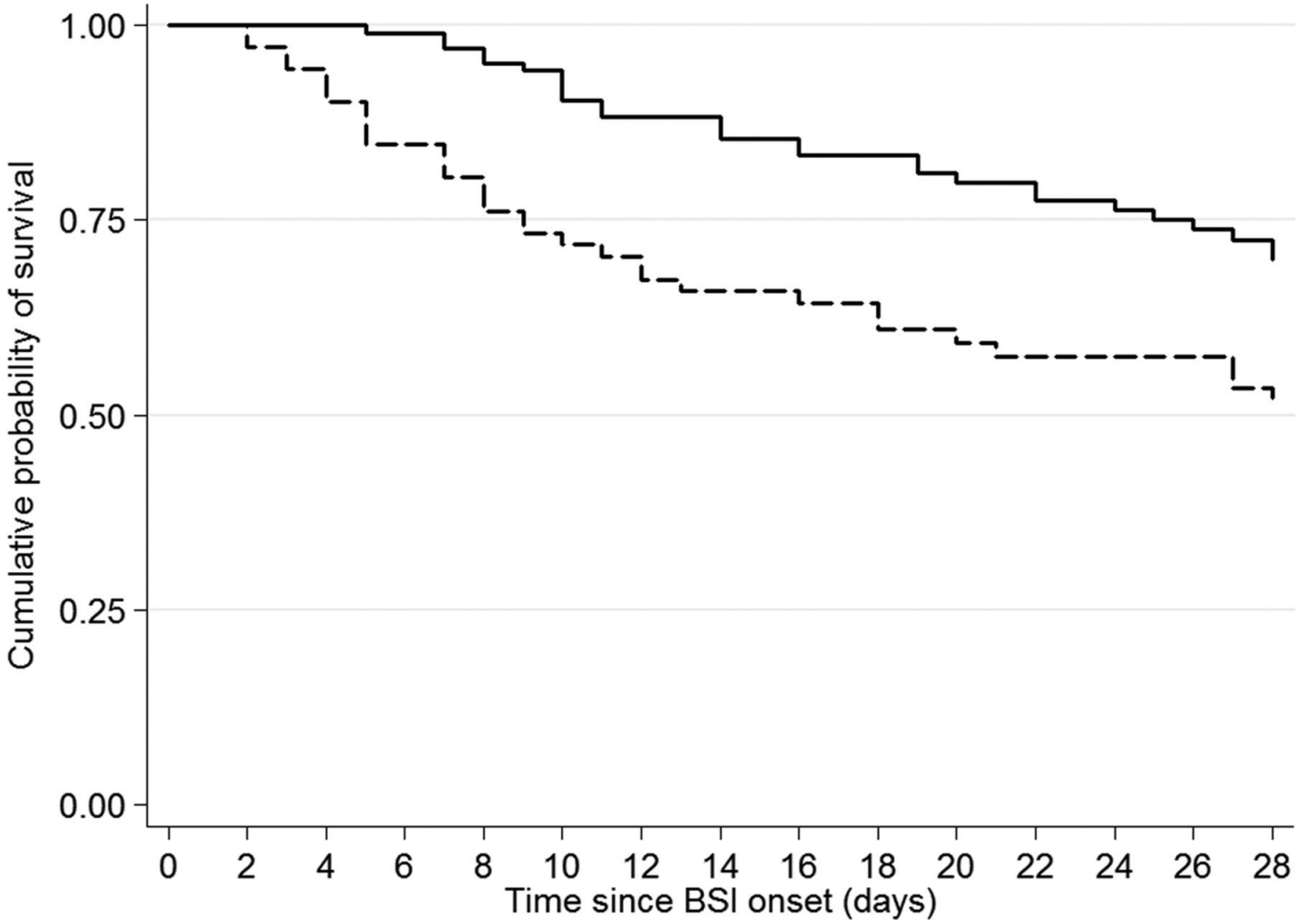
Expert Opin Pharmacother. 2016 April ; 17(6): 761–781.

Combination therapy for carbapenem-resistant Gram-negative bacteria



J Antimicrob Chemother. 2014;69(9):2305-2309.

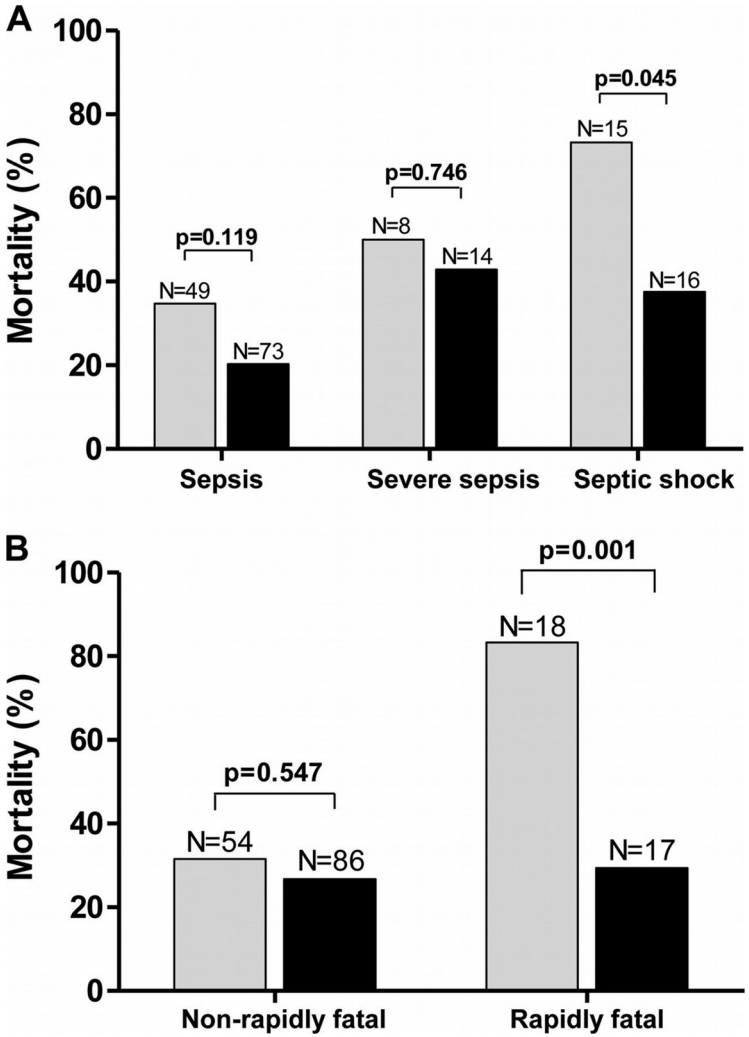
Kaplan-Meier survival estimates of patients with carbapenemase-producing K. pneumoniae bloodstream infections according to treatment regimen: combination therapy (continuous line) versus monotherapy (dotted line).



George L. Daikos et al. Antimicrob. Agents Chemother. 2014;58:2322-2328

Antimicrobial Agents and Chemotherapy

Graphic presentation of the effect of treatment (monotherapy [gray bars] versus combination therapy [black bars]) by severity of underlying disease (A) and by severity of sepsis (B).



George L. Daikos et al. Antimicrob. Agents Chemother. 2014;58:2322-2328

Antimicrobial Agents and Chemotherapy

Table 1. Overview of Carbapenemase Enzyme Types in *Enterobacteriaceae*

Ambler Class (Active Site)	Example Enzymes	Host Organisms	Enzyme Substrates					Inhibition by Currently Available β-Lactamase Inhibitors (Clavulanic Acid, Tazobactam, and Sulbactam)	Region Mostly Found In
			Penicillins	Narrow Spectrum Cephalosporins	Extended Spectrum Cephalosporins	Aztreonam	Carbapenems		
A (serine)	KPC-2 to 22	Mainly found in *Klebsiella pneumoniae* (have been identified in other *Enterobacteriaceae* and nonfermenters)	Yes	Yes	Yes	Yes	Yes	Variable[a]	United States and worldwide
B (Zinc binding thiol –"MBLs")	NMD-1 IMP-I VIM-1	*Enterobacteriaceae* and nonfermenters	Yes	Yes	Yes	No	Yes	No	Southern Asia
D (serine)	OXA-48	*Enterobacteriaceae* (other types of OXA carbapenemases mainly found in *Acinetobacter* spp.)	Yes	Yes	Weak Activity[b]	No	Minimal Hydrolysis[b]	No	Southern Europe

Open Forum Infectious Diseases 2015

DOI: 10.1093/ofid/ofv050

Potential Treatment Algorithm for Carbapenem-Resistant KPC-Producing Klebsiella pneumoniae

Infection Source	Empiric Treatment: Core Drugs	Empiric Treatment: Possible Adjunct Drugs	Antimicrobial Susceptibility Directed Treatment Considerations
Bloodstream	• High-dose meropenem or doripenem • And polymyxin B	• Aminoglycoside • Tigecycline • Fosfomycin • Rifampin	Meropenem/doripenem: • MIC ≤16 µg/mL continue high-dose meropenem/ doripenem • MIC >16 µg/mL consider alternative in vitro active antimicrobial[a] Polymyxin B/colistin: • MIC ≤ 2 µg/mL continue polymyxin B/colistin[b,c] • MIC >2 µg/mL consider alternative in vitro active antimicrobial If both meropenem/doripenem MIC (>16 µg/mL) and polymyxin B/colistin MIC (>2 µg/mL), then consider a high-dose tigecycline-based regimen or a dual dual carbapenem-based regimen[d,e] If pan-drug-resistant infection, select case-reports support dual carbapenem-based regimen[e] Tigecycline: • MIC ≤1 µg/mL consider tigecycline[d] • MIC >1 µg/mL consider alternative in vitro active antimicrobial Fosfomycin[f]: • MIC ≤32 µg/mL consider fosfomycin • MIC >32 µg/mL consider alternative in vitro active antimicrobial Amioglycoside: • MIC ≤2 µg/mL (Gentamicin/ Tobramycin) or ≤4 µg/mL (Amikacin) consider aminoglycoside • MIC >2 (Gentamicin/ Tobramycin) or >4 µg/mL (Amikacin) consider alternative in vitro active antimicrobial
Lung	• High-dose meropenem or doripenem • And polymyxin B	• Tigecycline • Aminoglycoside • Fosfomycin • Rifampin	
Gastrointestinal/ biliary tract	• High-dose meropenem or doripenem • And polymyxin B • And high-dose tigecycline	• Fosfomycin • Rifampin	
Urine	• High-dose meropenem or doripenem • And fosfomycin[g] • Or aminoglycoside[g]	• Colistin • Aminoglycoside	

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Drug in Late Stage (Phase 3) Clinical Development With Activity Against Carbapenem-Resistant Enterobacteriaceae

Drug	Class	Stage of Development	Carbapenemase Spectrum	Phase III Studies	Proposed Dose
Ceftazidime-avibactam	Cephalosporin-β-lactamase inhibitor	Phase 3	Activity against KPCs and OXA-48 (not active against MBLs)	• Ceftazidime-avibactam + metronidazole vs meropenem for cIAI • Ceftazidime-avibactam + metronidazole vs meropenem for NP • Ceftazidime-avibactam vs doripenem for cUTI	IV: 2000 mg (ceftazidime)/500 mg (avibactam) q8h
Ceftaroline-avibactam	Cephalosporin-β-lactamase inhibitor	Entering Phase 3	Active against KPCs and OXA-48 (not active against MBLs)	• Ceftaroline- avibactam vs doripenem for cUTI (Phase II study, proposed Phase III studies not yet available)	IV: 600 mg (ceftaroline)/600 mg (avibactam) q8h
Plazomicin	Aminoglycoside	Phase 3	Active against most KPCs (not active against many NDMs)	• Plazomicin vs colistin when combined with a second antibiotic (either meropenem or tigecycline) for CRE BSI or NP	IV: 10–15 mg/kg q24h
Eravacycline	Tetracycline	Phase 3	Active against KPCs	• Eravacycline vs ertapenem for cIAI • Eravacycline vs levofloxacin for cUTI	IV: 1.0 mg/kg q12h or 1.5 mg/kg q24h PO: 200–250 mg q12h

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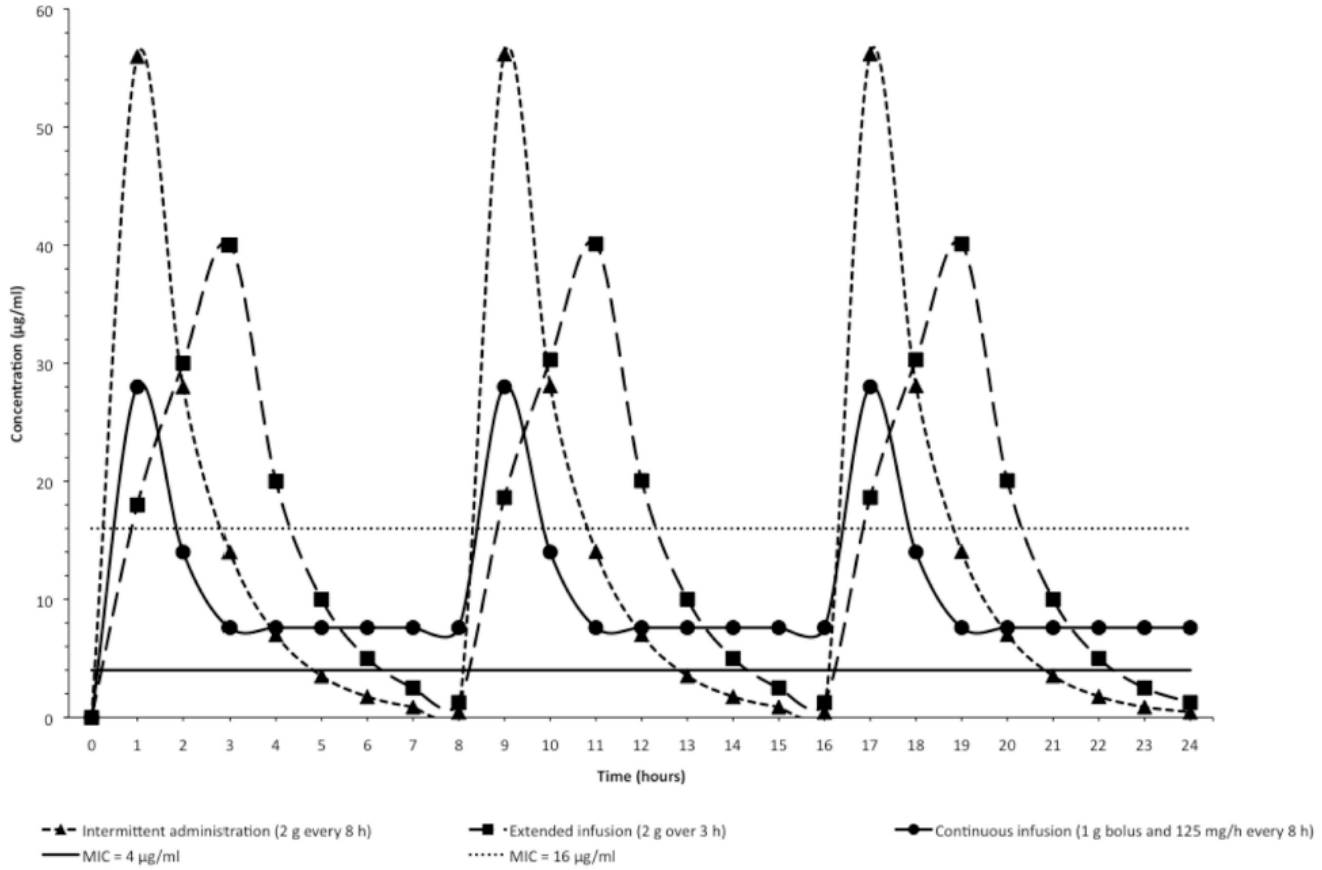

Figure 5.

Concentration of meropenem (in µg/ml) over time (in hours) when administered as an intermittent (triangle), extended (square), or continuous (circle) infusion (derived from Nicolau [166], Dandekar *et al.* [167] and Krueger et al.[168]. Continuous line represents MIC = 4 µg/ml, and dotted line MIC = 16 µg/ml. Note that only an extended infusion may result in sufficiently elevated serum meropenem concentrations when isolates approach MIC of 16 µg/ml. Antibiotics that permeabilize the bacterial cell membrane (e.g. polymyxins), interfere with cell wall synthesis (e.g. fosfomycin), or inhibit protein synthesis (e.g. aminoglycosides or tigecycline) may decrease the MIC sufficiently so that it is exceeded when a carbapenem is co-admininstered as a prolonged (continuous or extended) infusion, thereby achieving satisfactory microbiological and clinical outcomes.

Expert Opin Pharmacother. 2016 April ; 17(6): 761–781.

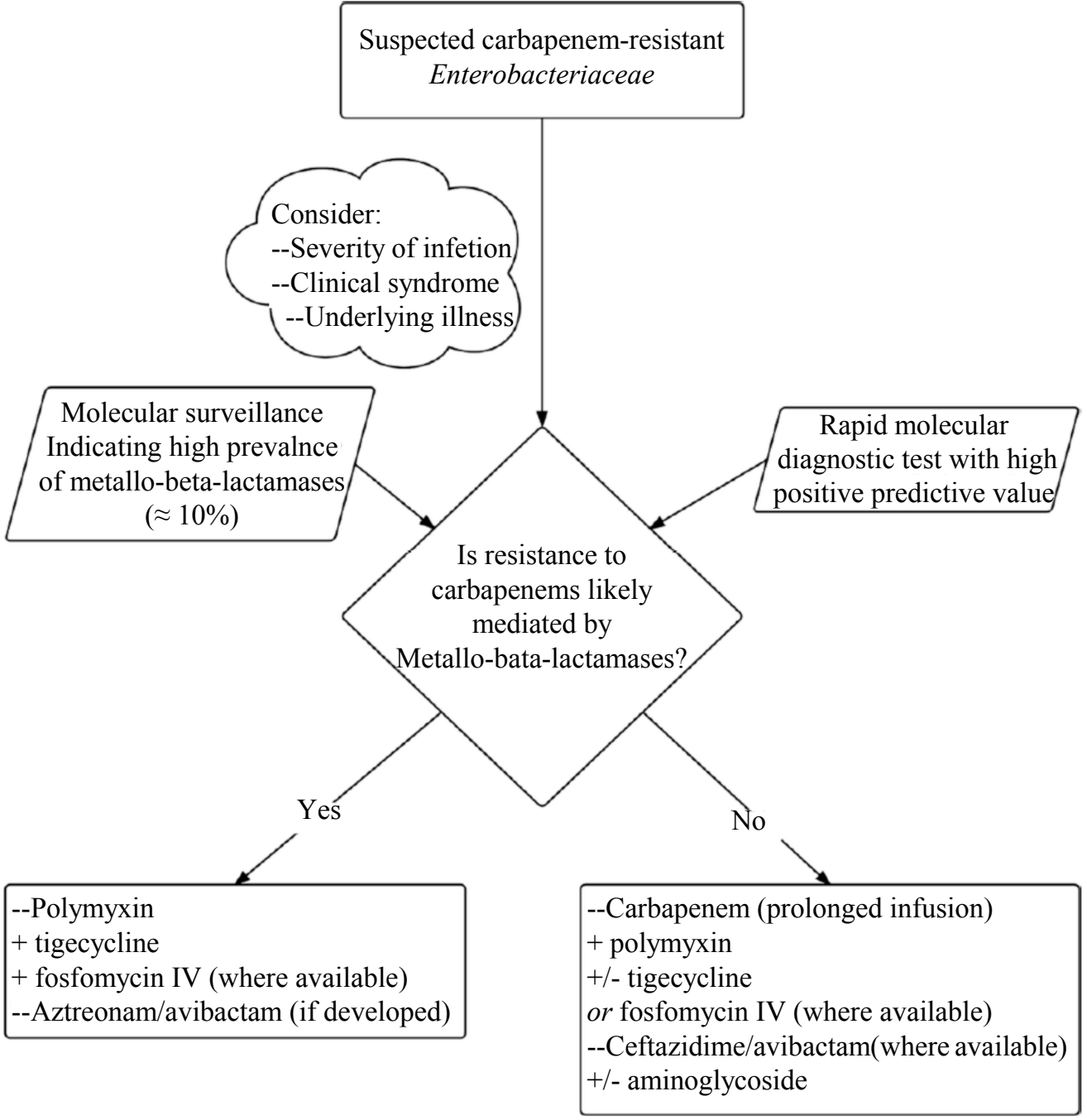

Figure 7.
Guide for the empiric treatment of infections where carbapenem-resistant

Expert Opin Pharmacother. 2016 April ; 17(6): 761–781.

Summary

- Carbapenemase-producing Enterobacteriaceae (CPE) was <10% in Taiwan
- A benefit for combination therapy, especially carbapenem-containing regimens against isolates where the carbapenem MIC is < 16 μg/ml and where carbapenems are administered in high doses and prolonged infusion (observational data)
- Currently available antibiotics reliable (> 85% activitiy) against CRE include polymyxin B and colistin, tigecycline, fosfomycin and aminoglycosides

This document does not provide recommendations regarding indications for the use of CP. It is intended for acute-care hospitals that already use CP, and it addresses when and under what circumstances CP may be discontinued.

Infect Control Hosp Epidemiol. **2018** Feb;**39**(**2**):127-144

Multidrug-Resistant Enterobacteriaceae (MDR-E, such as ESBL-E and/or CRE)

- Maintaining CP for ESBL-E and CRE for the duration of the index hospital stay when infection or colonization with these bacteria is first detected.
- We recommend that for extensively drug-resistant Enterobacteriaceae, such as carbapenemase-producing CRE, or Enterobacteriaceae with very limited treatment options (susceptible to ≤2 antibiotic classes used to treat that organism), hospitals should maintain CP indefinitely.

Multidrug-Resistant Enterobacteriaceae (MDR-E, such as ESBL-E and/or CRE)

Considering discontinuation of CP on a case-by-case basis

(1)at least 6 months have elapsed since the last positive culture;

(2) presence of a clinical infection and ongoing antibiotic use, where discontinuation of CP should be discouraged in the setting of suspected or known infection with ESBL-E or CRE, and concurrent broadspectrum antibiotic use that may select for these organisms

(3) procurement of an adequate number of screening samples, with at least 2 consecutive negative rectal swab samples obtained at least 1 week apart to consider an individual negative for ESBL-E or CRE colonization.

TABLE 1. Israeli National Guidelines for the Care of Patients with Carbapenem-Resistant Enterobacteriaceae in Acute-Care Versus Post-Acute-Care Hospitals[a]

		Post-Acute-Care Hospitals	
Variable	Acute-Care Hospitals	Skilled Nursing/Chronic Ventilated/ Subacute Wards	Rehabilitation Wards
Room assignment	Private or cohorting with other CRE carriers	Private or cohorting with other CRE carriers	No regulation regarding room assignment
Dedicated nursing staff for CRE carriers	Required	Not required	Not required
Use of gloves and gowns in care of CRE carriers	Mandatory on room entrance	Mandatory on room entrance	According to standard precautions
Admission CRE screening of high-risk groups[b]	Required	Required	Not required, except in outbreak setting
CRE screening of patient contacts	Required	Required	Required
Participation in group activities	Prohibited	Allowed	Allowed
Standard protocol for discontinuation of contact isolation	Yes	Yes	Yes
Regular mandatory census reporting to NCIC	Yes	Yes	Yes

1. General guidelines for the process of discontinuing carrier status

   1.1. The duration of carriage is >1 month in most cases. Therefore, negative results within <1 month after a positive culture may reflect insufficient test sensitivity.
   1.2. As a rule, CPE testing for the purpose of discontinuing carrier status should not be undertaken <1 month after the positive culture.
   1.3. The infection prevention staff in each facility is responsible for making decisions about individual cases and for setting the general policy regarding discontinuation of carrier status.

CRE Definition

- Enterobacteriaceae that are nonsusceptible (i.e., intermediate or resistant) to a carbapenem
  - Imipenem
  - Meropenem
  - Ertapenem
  - Doripenem

Trends in resistance of *K. pneumoniae, E.coli, E. cloacae* to carbapenems

	Resistant no./total no. (%)								
	Klebsiella pneumoniae			*E. coli*			*Enterobacter cloacae*		
Year (no.)	imipenem	ertapenem	or	imipenem	ertapenem	or	imipenem	ertapenem	or
2017(1-5)	41/495 (8.3)	37/495 (7.5)	58/495 (11.7)	25/1380 (1.8)	27/1380 (2.0)	41/1380 (3.0)	23/140 (16.4)	19/140 (13.6)	35/140 (25)
2016	63/1195 (5.3)	26/1195 (2.2)	72/1195 (6.0)	6/3276 (0.2)	31/3276 (0.9)	35/3276 (1.1)	61/359 (17.0)	45/359 (12.5)	99/359 (27.6)
2015	75/1225 (6.1)	50/1225 (4.1)	111/1225 (9.1)	22/3260 (0.7)	38/3260 (1.2)	50/3260 (1.5)	50/342 (14.6)	41/342 (12.0)	80/342 (23.4)
2014	49/1168 (4.2)			9/3146 (0.3)			45/350 (12.9)		
2013	44/1202 (3.7)			16/2961 (0.5)			73/368 (19.8)		
2012	30/1225 (2.4)			13/3027 (0.4)			11/326 (3.4)		
2011	22/1125 (2.0)			11/2776 (0.4)			12/307 (3.9)		
2010	18/1182 (1.5)			9/2884 (0.3)			7/316 (2.2)		
2009	23/1263 (1.5)			21/2777 (0.8)			6/348 (1.7)		
2008	28/1246 (2.2)			39/2734 (1.4)			11/340 (3.2)		
2007	28/1075 (2.6)			15/2463 (0.6)			8/260 (3.1)		

2017 CLSI M100-S27 criteria: ETP >=1; IPM >=2

泛抗藥性菌種感染管制措施修改政策後差異比較：

項目	改變前	改變後	變更
CRE 政策	1. 只發 CRE ，檢驗報告註抗藥性菌，加強洗手	1. 加入 carbapenemase 檢驗，陽性病人採接觸隔離 2. carbapenemase 陽性，陽性菌株須通報 CDC 檢驗	1. 加入 carbapenemase 檢驗，陽性病人採接觸隔離 2. carbapenemase 陽性，陽性菌株須通報 CDC 檢驗

解除隔離

項目	改變前	改變後	變更
CRE	需於臨床抗生素治療結束後 72 小時，原發陽性部位及肛門拭紙，1-2 週內不同日採檢 1 次，當檢驗結果皆呈陰性	需於臨床抗生素治療結束後 72 小時，原發陽性部位一套及肛門拭子 *3 套，1-2 週內不同日採檢 3 次，當檢驗結果皆呈陰性 (CDC 手冊)	1. Carbapenemase 陽性，若原發部位為血液、尿液、傷口等，採檢 1 套原發部位陰性，3 套肛門拭子陰性 (每週一套 *3) 2. Carbapenemase 陰性，原部位一套若未長即可解除
MRSA	無解除註記機制	採原部位一套若未長 ORSA 及可解除	採原部位一套若未長 ORSA 即可解除
C. difficile	1. 至少連續 48 小時無症狀（無腹瀉且解正常或成型變）且腸蠕動恢復正常。 2. 若 *C. difficile* 細菌培養陽性者另除上述條件之外，尚須至少追蹤一套 *C. difficile* 細菌培養呈陰性，始可撤除隔離。	至少連續 48 小時無症狀（無腹瀉且解正常或成型變）	取消第 2 項細菌培養複驗陰性再解除