Comprehensive
Infectious
Disease
Center

11. Symposium
Infektionsmedizin in Tübingen
Neue Entwicklungen in der Infektionsmedizin
01. und 02. März 2013

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THERAPY AND PREVENTION OF MULTIDRUG RESISTANT INFECTIONS

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Impact of Routine Infectious Diseases Service Consultation on the Evaluation, Management, and Outcomes of *Staphylococcus aureus Bacteremia*

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Table 4. Evaluation and classification of *Staphylococcus aureus* bacteremia by time period.

Variable	Before routine consultation (n = 134)	During routine consultation (n = 100)	P
Infectious diseases consultation	71 (53)	90 (90)	<.001
Time to consultation, median days (IQR)	3 (1–5)	2 (1–3)	.005
Duration of patient follow-up, median days (IQR)	60 (31–81)	54 (35–71)	.19[a]
Echocardiogram obtained			
Overall	77 (57)	73 (73)	.01
Transthoracic	74 (55)	69 (69)	.03
Transesophageal	24 (18)	23 (23)	.34
Both	21 (16)	19 (19)	.50
Radiographic study obtained			
Overall	109 (81)	91 (91)	.04
Vascular imaging	44 (33)	44 (44)	.08
Body imaging	87 (65)	76 (76)	.07
Head imaging	51 (38)	29 (29)	.15
Spine imaging	21 (16)	21 (21)	.29
Nuclear imaging	5 (4)	3 (3)	1[b]
Infective endocarditis			
Total	31 (23)	33 (33)	.09
Definite, proportion (%) of patients	7/31 (23)	12/33 (36)	
Possible, proportion (%) of patients	24/31 (77)	21/33 (64)	
Early metastatic infection			
Overall	33 (25)	36 (36)	.06
Vertebral osteomyelitis	9 (7)	13 (13)	.10
Deep-tissue infection or abscess	11 (8)	11 (11)	.47
Septic pulmonary emboli	10 (7)	10 (10)	.49
Septic arthritis	8 (6)	10 (10)	.25
Epidural infection or abscess	4 (3)	9 (9)	.05
Deep-vein septic thrombophlebitis	5 (4)	7 (7)	.26
Visceral abscess	4 (3)	1 (1)	.40[b]
Nonvertebral osteomyelitis	1 (1)	1 (1)	.49[b]
Endocarditis or early metastatic infection	44 (33)	46 (46)	.04

Jenkins, CID 2008

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Every Monday in Germany there is a flight crash with 35 dead people

GERMANY: MRSA BSI (2007)	GERMANY: 3GCR-E.COLI (2007)
Number: 2,484 (1,383–4,128)	Number: 1,921 (964–3,410)
Incidence (x100.000 inhabitans): 3.0 (1.7–5)	Incidence (x100.000 inhabitans): 2.3 (1.2–4.1)
Excess mortality : 493 (220-924)	Excess mortality : 343 (65-860)

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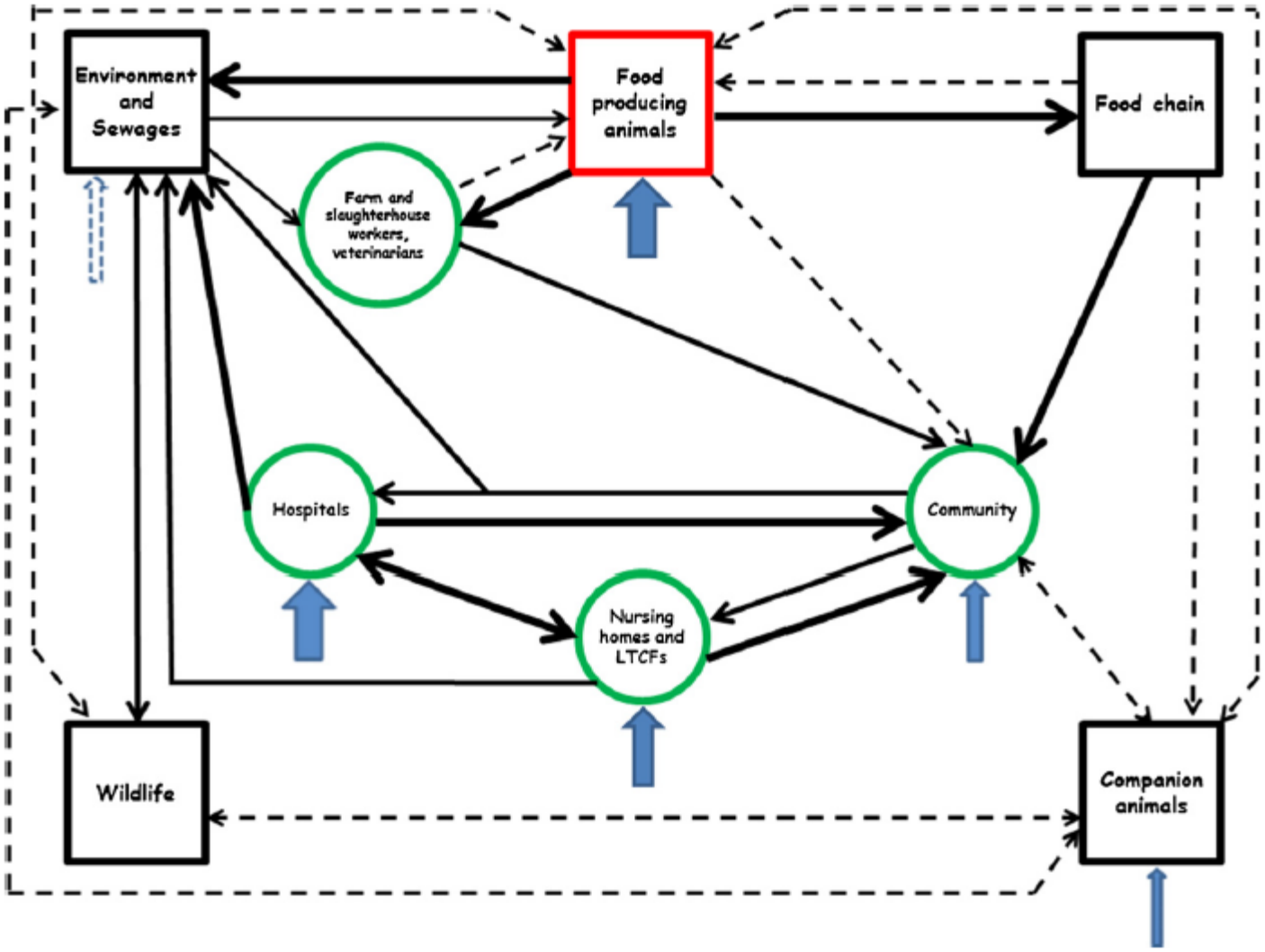
Extended-spectrum cephalosporin-resistant gram-negative organisms in livestock: An emerging problem for human health?



Seiffert, Drug Res Update, in press

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Diversity and assessment of potential risk factors of Gram-negative isolates associated with French cheeses

Family	Antibiotic	% Resistant strains
Aminosids	AN	15
	GM	20
	TM	32
Penams	TCC	25
	PIP 75	29
	TZP 85	31
	AMC	41
	TIC	47
	AMX	51
	AM	65
	MEC	87
Imipenems	IPM	23
Monobactams	ATM	73
Cephems	CAZ	48
	CF	67
	CTX	67
Fosfomycins	FOS 50	65
Quinolons	NA	21
	CIP	30
Colistin	CS 50	62
Phenicols	C	56
Tetracyclins	TE	46
Rifamycins	RA 30	34
Sulfamids	SSS 200	56

Coton, Food Micr 2012

Road map

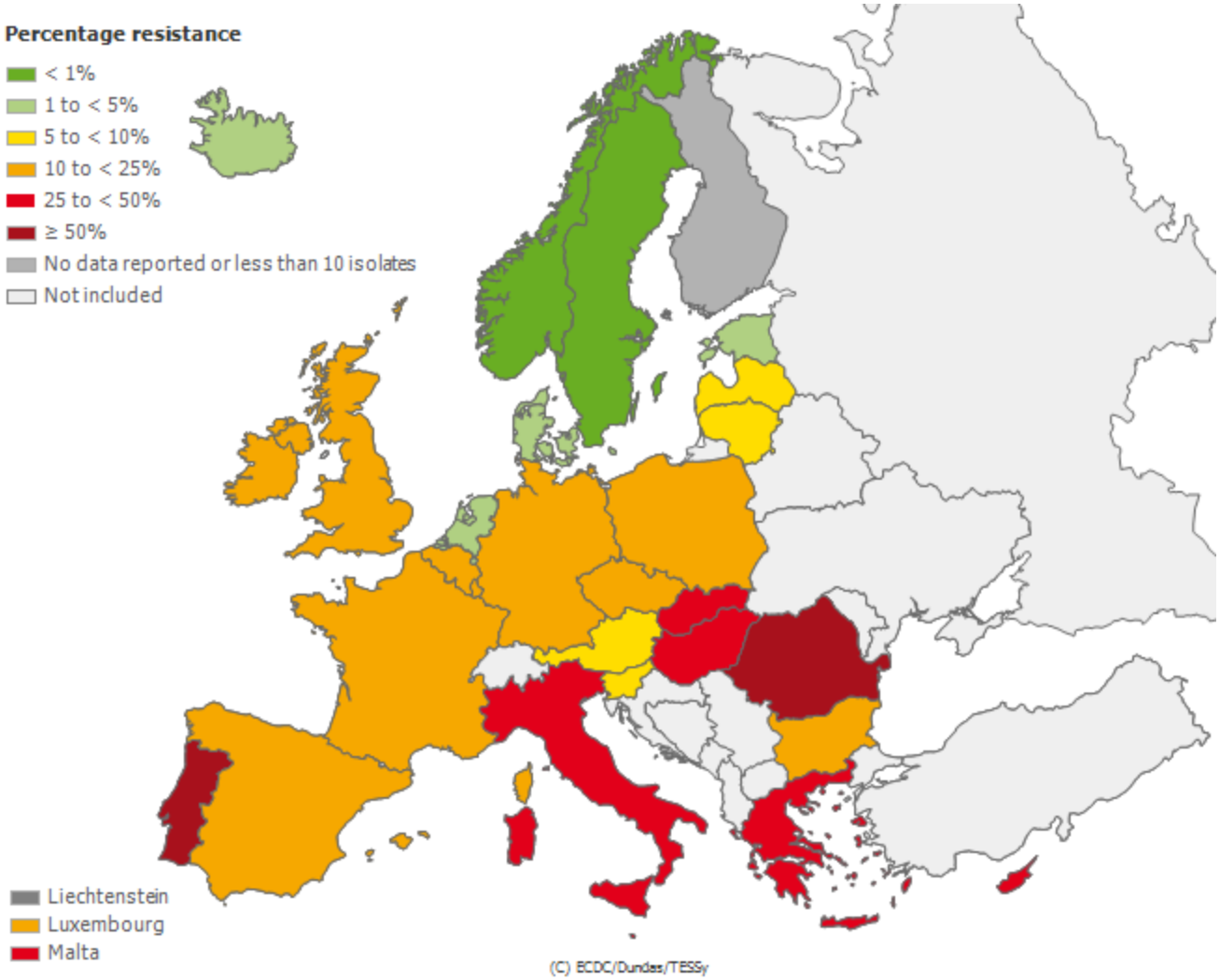
Prevention

- Update on incidence
- Screening
- Decolonisation
- Clorhexidine
- Anibiotic stewardship

Therapy

- Single vs combination
- Indications
- MRSA
- CRE

Proportion of Methicillin Resistant *Staphylococcus aureus (MRSA)* Isolates in Participating Countries in 2011



MRSA and Germany

- There are about 132 000 cases of MRSA in German hospitals each year.
- MRSA is found in about 18% to 20% of all inpatient-derived culture specimens that are positive for S. aureus.
- CA-MRSA is not yet endemic in Germany
- Important risk factors for its acquisition include travel to high-prevalence areas and household contact with persons that harbor a CA-MRSA infection.

Kock R, Dtsch Arztebl Int 2011

Figure 4.9: *Klebsiella pneumoniae*: percentage (%) of invasive isolates with resistance to third-generation cephalosporins, by country, EU/EEA countries, 2011

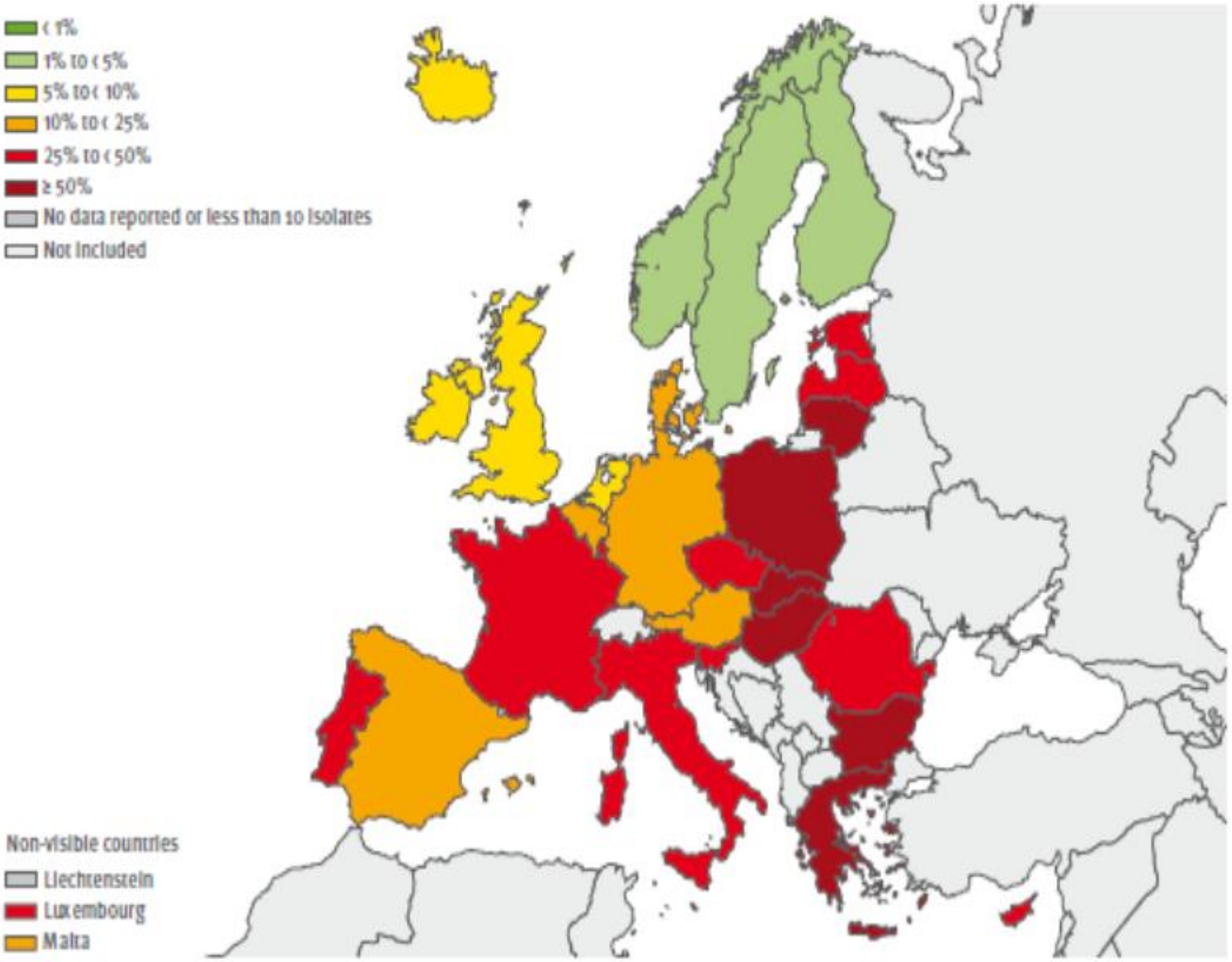
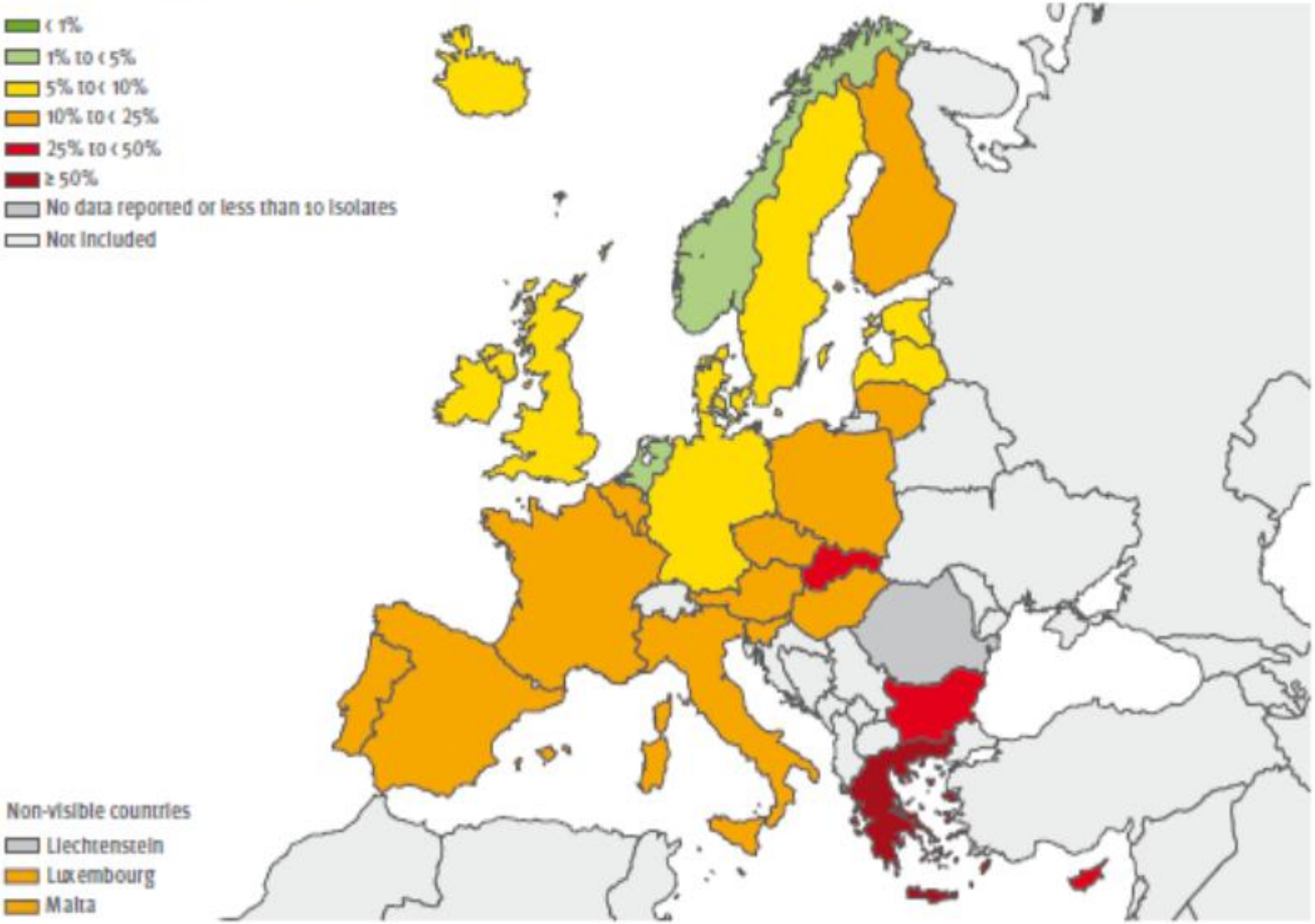


Figure 4.23: ***Pseudomonas aeruginosa*****: percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2011**



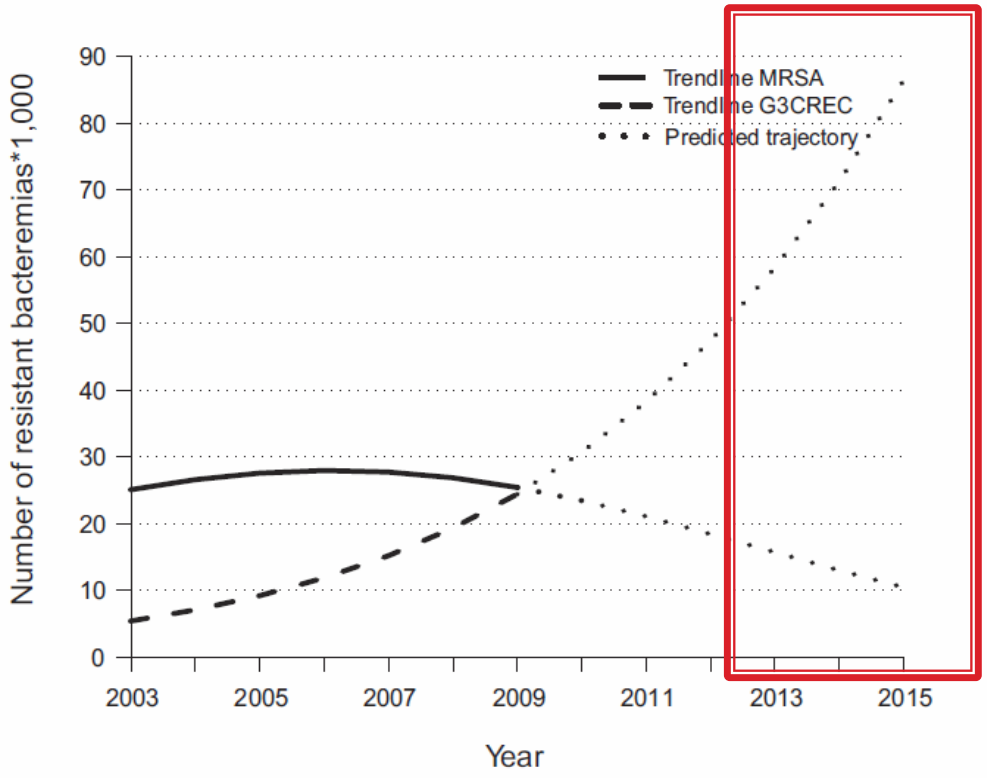


Figure 1. Trends in the estimated number of MRSA and G3CREC bacteremias in the European region. Extrapolated EARSS numbers for 2003–2009, and future trajectories based on regression analysis for 2010–2015.
doi:10.1371/journal.pmed.1001104.g001

de Kraker, PLoS Med 11 Oct 2011

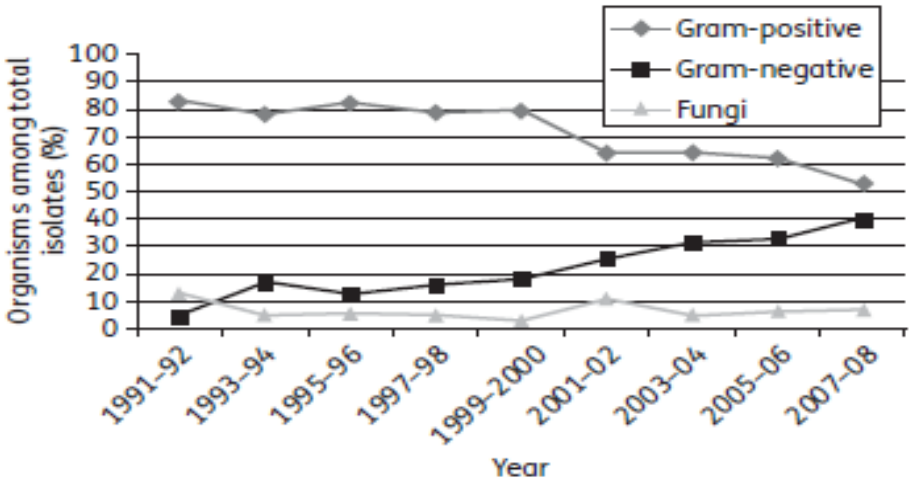


Figure 1. Trends in the aetiology of CRBSIs from 1991 to 2008.

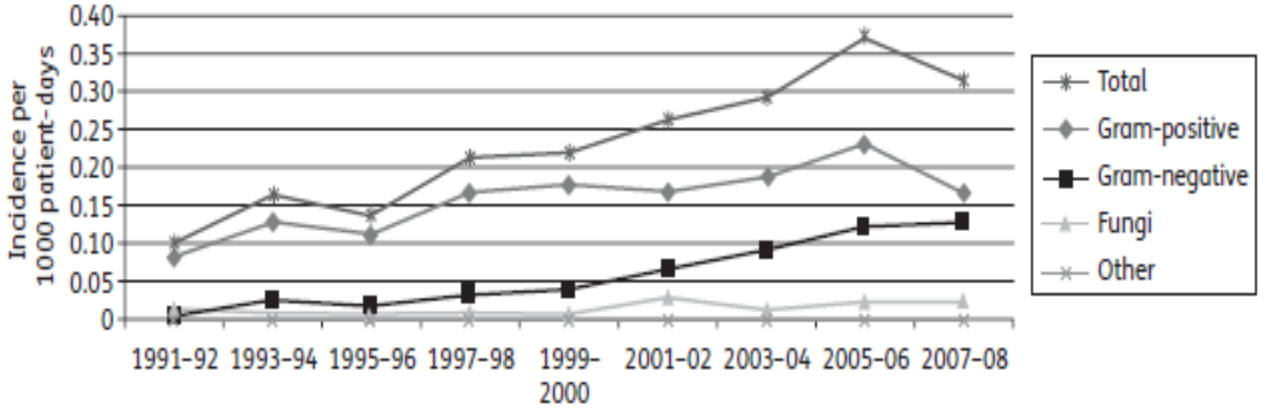


Figure 2. CRBSI incidence/1000 patient-days.

Marcos JAC 2011

BSI in Australia (2001-2009)

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- The proportion of gram negative isolates increased
  - 44% to 53%, P = 0.006
- Gram positives decreased
  - 49% to 45%, P = 0.045
- Significant in community onset infections
- **Gram negative pathogens were most prevalent amongst the elderly** (53% in the ≥70 years age group, P <0.0001 vs 41% in the ≥20 to <70 years age group), attributable to an age-dependent increase in Escherichia coli infections and a decrease in Staphylococcus aureus infections (P<0.0001 for both).

Aung, Commun Dis Intell 2012 Dec

Preliminary Results (IT) – Primary outcome

	Colonisation at hospital admission n = 5378
MRSA	**140 (2.6%)**
ESBL+	**779 (14.5%)**
E. coli	646
K. pneumoniae	86
Proteus/Morganella	39
Serratia	8
CRE	**96 (1.8%)**
E. coli	19
K. pneumoniae	77

Long-Term Risk for Readmission in MRSA+

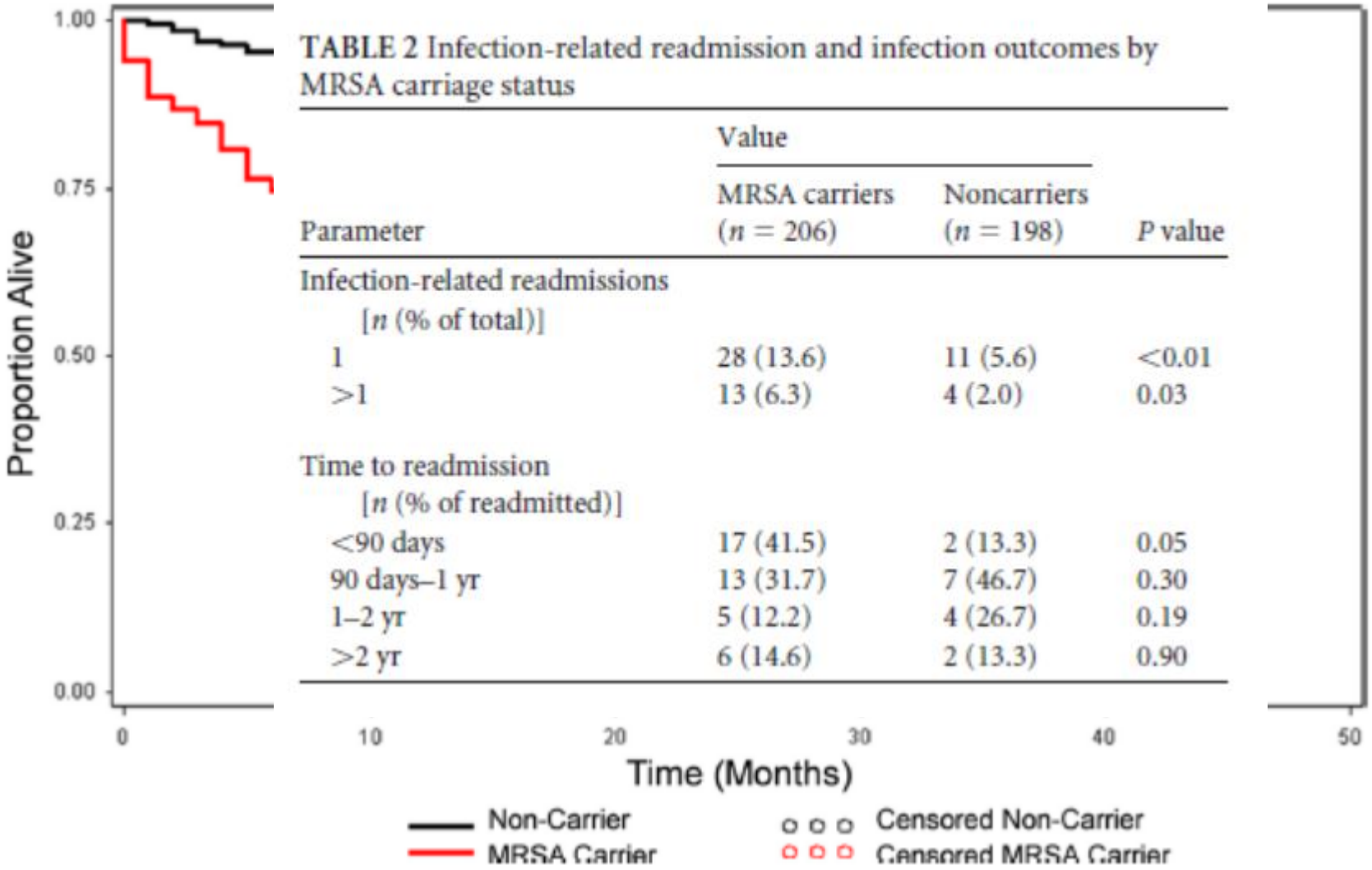

TABLE 2 Infection-related readmission and infection outcomes by MRSA carriage status

Parameter	Value: MRSA carriers ($n = 206$)	Value: Noncarriers ($n = 198$)	P value
Infection-related readmissions [n (% of total)]			
1	28 (13.6)	11 (5.6)	<0.01
>1	13 (6.3)	4 (2.0)	0.03
Time to readmission [n (% of readmitted)]			
<90 days	17 (41.5)	2 (13.3)	0.05
90 days–1 yr	13 (31.7)	7 (46.7)	0.30
1–2 yr	5 (12.2)	4 (26.7)	0.19
>2 yr	6 (14.6)	2 (13.3)	0.90

FIG 1 Kaplan-Meier survival plot for MRSA carriers and noncarriers.

Quezada AAC 2012

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Table 2. Sources of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infection in Year Following Detection of Carriage.

	No. (%) of Infections		
Infection Classification	**Total**	**Pre-Discharge***	**Post-Discharge**
Total	317 (100%)	132 (100%)	185 (100%)
Pneumonia†	109 (34%)	54 (42%)	55 (29%)
Skin and Soft Tissue†	84 (27%)	25 (19%)	59 (31%)
Primary Bloodstream	56 (18%)	28 (22%)	28 (15%)
Surgical Site	18 (6%)	9 (7%)	9 (5%)
Bone and Joint†	17 (5%)	2 (2%)	15 (8%)
Urinary Tract	10 (3%)	1 (1%)	9 (5%)
Gastrointestinal	7 (2%)	3 (2%)	4 (2%)
Other‡	16 (5%)	10 (8%)	6 (3%)
Associated Bacteremia	82 (26%)	33 (25%)	49 (26%)

Huang, PLOS one 2011

Scotland challenges the UK..
Targeted vs Universal

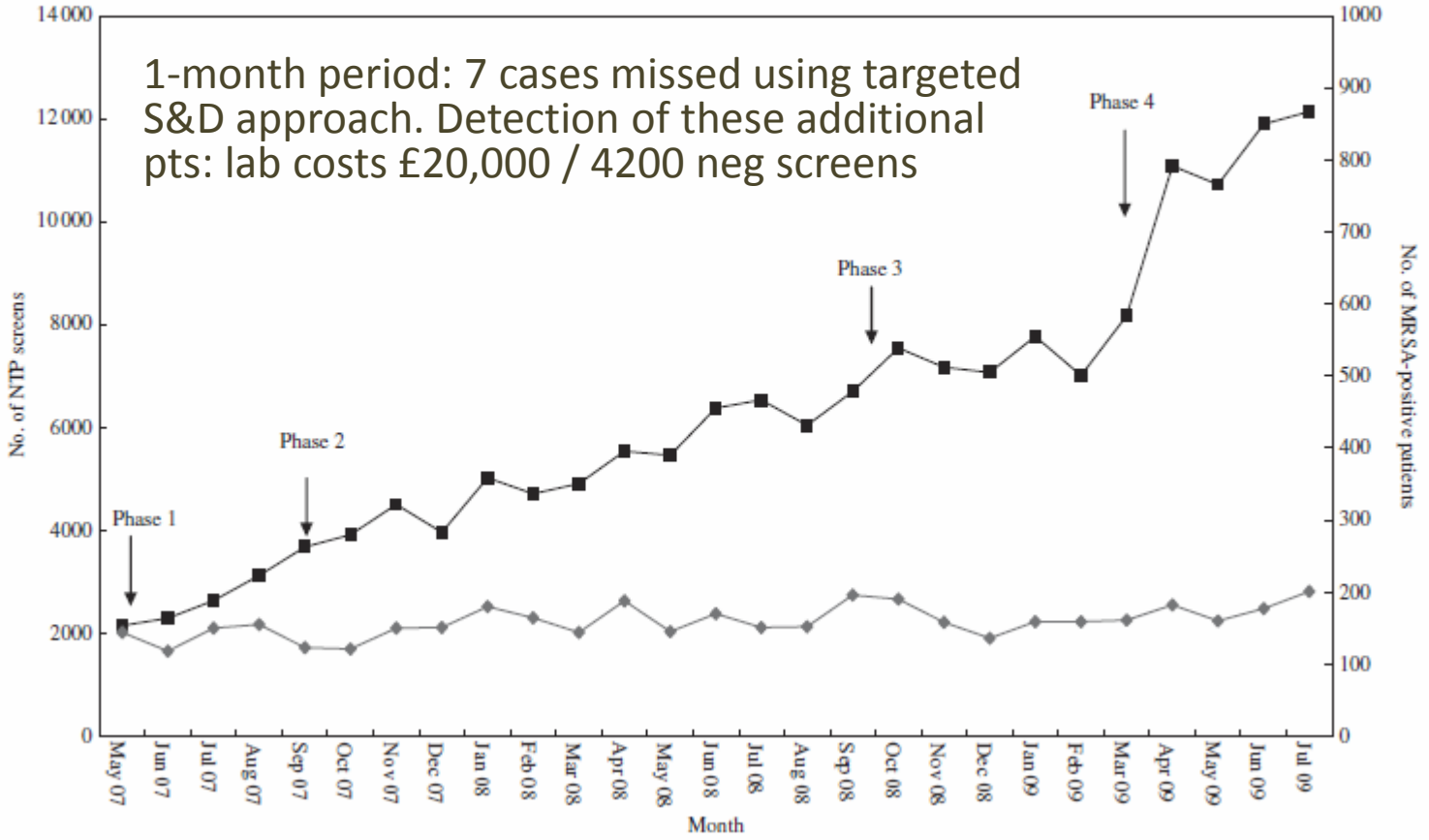

Table 2. Multivariable model of risk factors for patients with an always or intermittently colonized compared to a never colonized nasal MRSA carriage pattern at 30 days.

Variable	Odds Ratio	95% CI	P Value
Age 70 or less	0.61	(0.54; 0.68)	<.001
Acute care/past year	1.77	(1.56; 2.01)	<.001
Long term care/past year	2.82	(2.28;3.49)	<.001
Diabetes	1.22	(1.09;1.37)	<.001
Renal Disease	1.47	(1.22;1.77)	<.001
Decubitus ulcer	5.33	(3.71;7.66)	<.001
Any antibiotic use/past 6 months	1.35	(1.21;1.51)	<.001

doi:10.1371/journal.pone.0053674.t002

Gupta K, Martinello RA, Young M, Strymish J, et al. (2013) MRSA Nasal Carriage Patterns and the Subsequent Risk of Conversion between Patterns, Infection, and Death. PLoS ONE 8(1): e53674. doi:10.1371/journal.pone.0053674
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0053674

VRE positive patients at hospital admission

Table 3. Risk index score for recovery of vancomycin-resistant enterococci at hospital admission, by associated risk factor.

Risk factor	Point value
Previous recovery of MRSA[a]	4
Long-term hemodialysis	3
Transfer from LTCF or hospital	3
Exposure to ≥2 antibiotics[b]	3
Previous hospitalization[a]	3
Age >60 years	2

Tacconelli, CID 2004

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 7, 2010 VOL. 362 NO. 1

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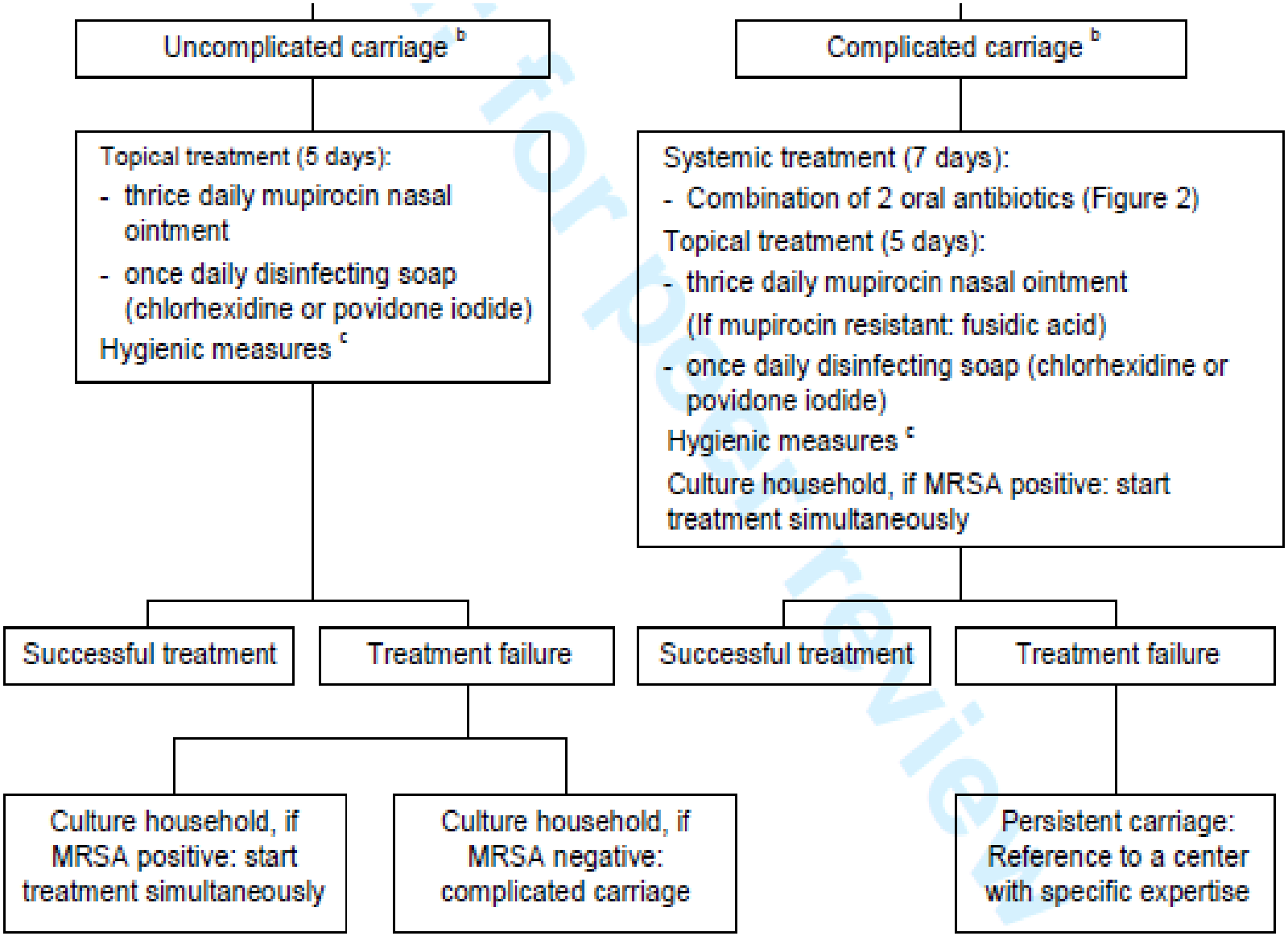
Table 2. Relative Risk of Hospital-Acquired *Staphylococcus aureus* Infection and Characteristics of Infections (Intention-to-Treat Analysis).

Variable	Mupirocin–Chlorhexidine (N=504)	Placebo (N=413)	Relative Risk (95% CI)*
	no. (%)		
S. aureus infection	17 (3.4)	32 (7.7)	0.42 (0.23–0.75)
Source of infection†			
Endogenous	12 (2.4)	25 (6.1)	0.39 (0.20–0.77)
Exogenous	4 (0.8)	6 (1.5)	0.55 (0.16–1.92)
Unknown	1 (0.2)	1 (0.2)	
Localization of infection			
Deep surgical site‡	4 (0.9)	16 (4.4)	0.21 (0.07–0.62)
Superficial surgical site‡	7 (1.6)	13 (3.5)	0.45 (0.18–1.11)
Lower respiratory tract	2 (0.4)	2 (0.5)	0.82 (0.12–5.78)
Urinary tract	1 (0.2)	0	
Bacteremia	1 (0.2)	1 (0.2)	
Soft tissue	2 (0.4)	0	

Bode et al., NEJM 2010



Ammerlaan HS, JAC 2011

High risk wards: surgery patients
MRSA bundle

1. MRSA nasal screening upon admission
1. Contact isolation
2. Hand hygiene
3. Cultural campaign
4. Outcome measures

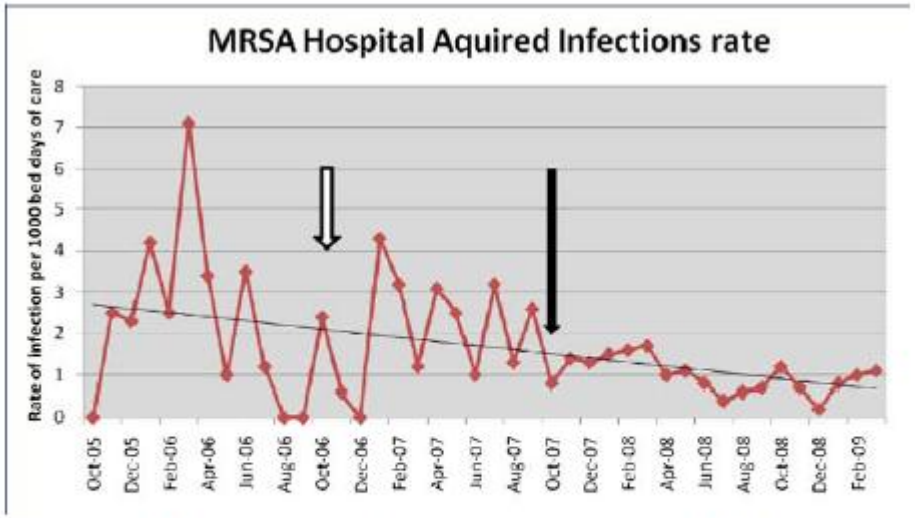


Figure 1 Variations of MRSA infection rate per 1,000 bed-days of care. Short white arrow: MRSA bundle implementation in 1 U. Long black arrow: hospital-wide MRSA bundle implementation.

Awad, ICHE, 2009
Thompson, AJIC 2013 Jan

Type of tests
Molecular vs Nothing

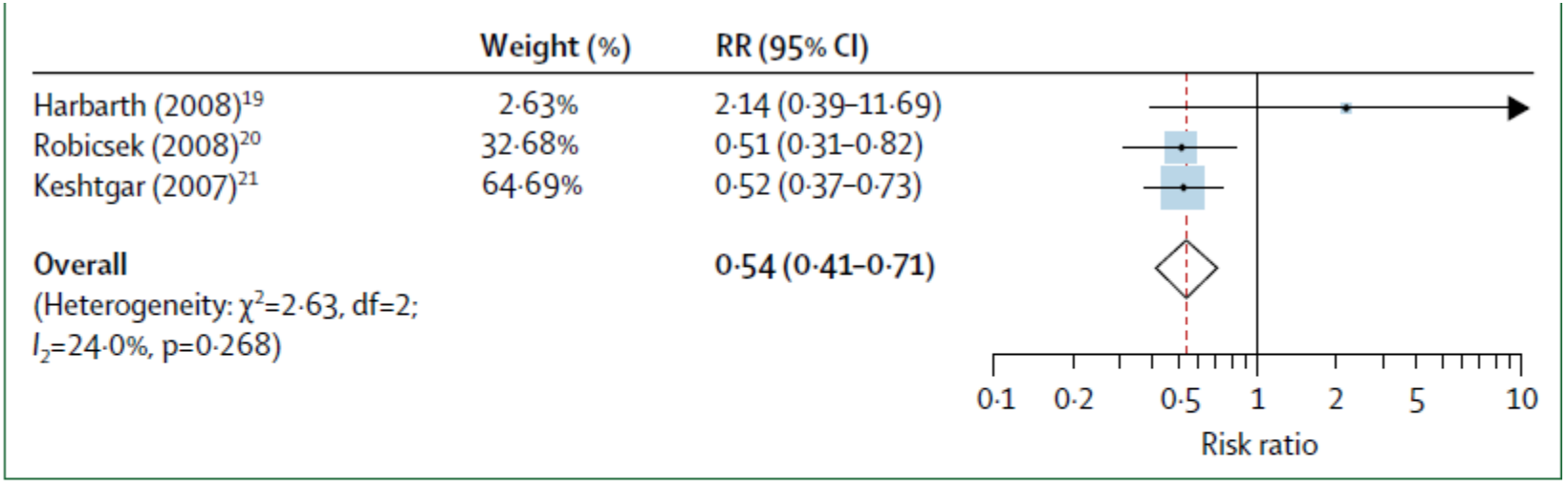


Figure 3: Effect of rapid molecular tests for meticillin-resistant *Staphylococcus aureus* (MRSA) at hospital admission on the incidence of MRSA bloodstream infections per 1000 patient-days

Comparison is between units in which screening was done by molecular tests and units in which screening was not done at all. Risk ratios (RR) and their 95% CIs are shown (fixed effects). Dotted line indicates combined RR. Squares indicate point estimates and the size of the square indicates the weight of each study in the meta-analysis.

Tacconelli, Lancet Infect Dis, 2009

Type of tests
Molecular vs Cultures

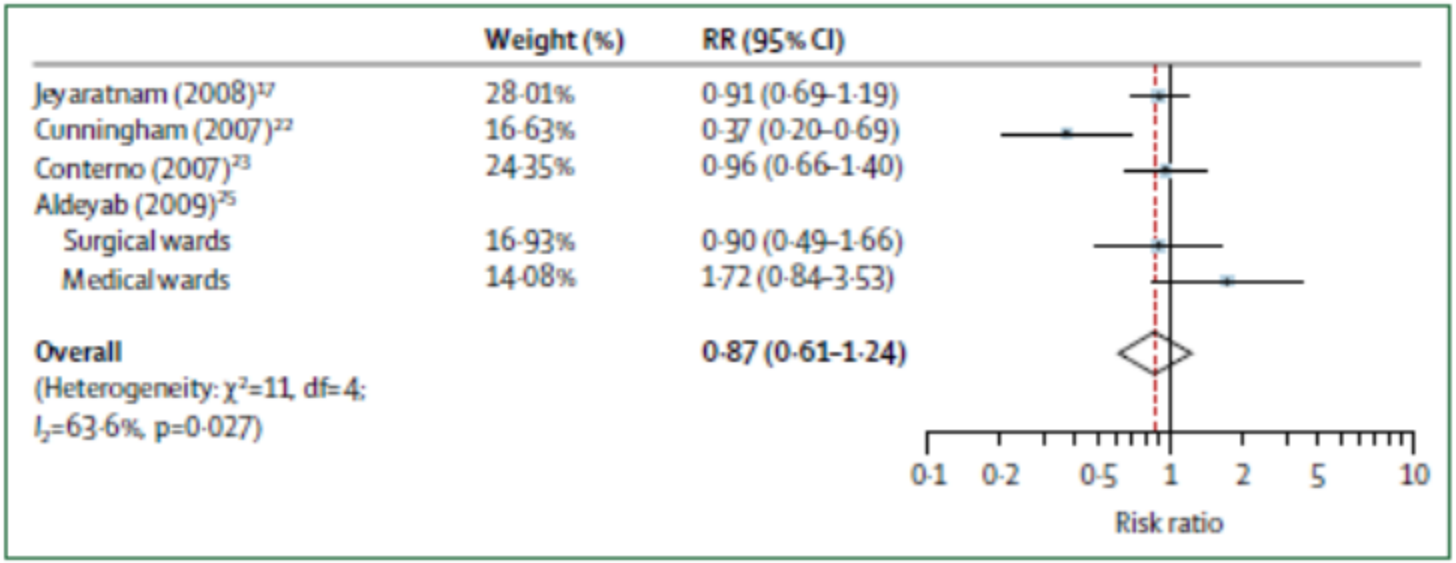
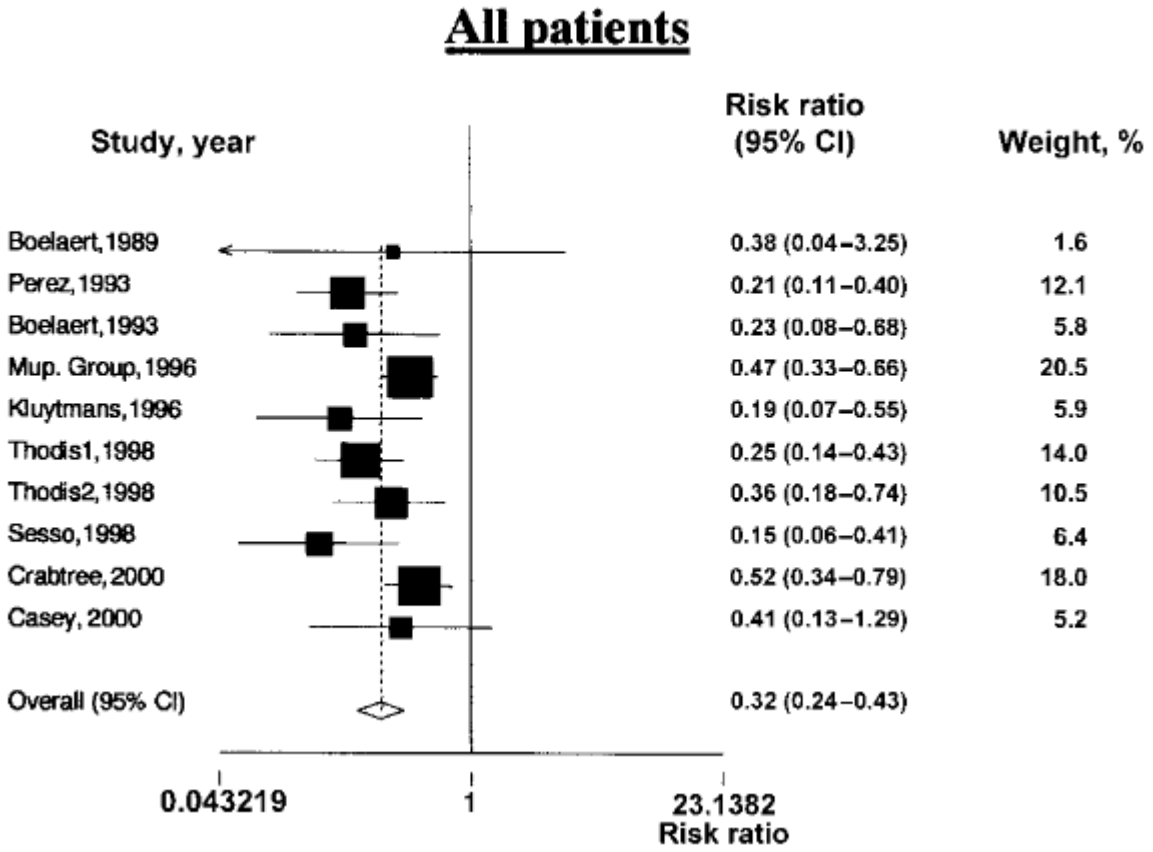


Figure 2: **Effect of rapid molecular tests for meticillin-resistant *Staphylococcus aureus* (MRSA) at hospital admission on MRSA acquisition rate per 1000 patient-days**

Comparison is between units in which screening was done by molecular tests and units in which screening was done by culture alone. Risk ratios (RR) and their 95% CIs are shown (random effects). Dotted line indicates combined RR. Squares indicate point estimates and the size of the square indicates the weight of the each study in the meta-analysis.

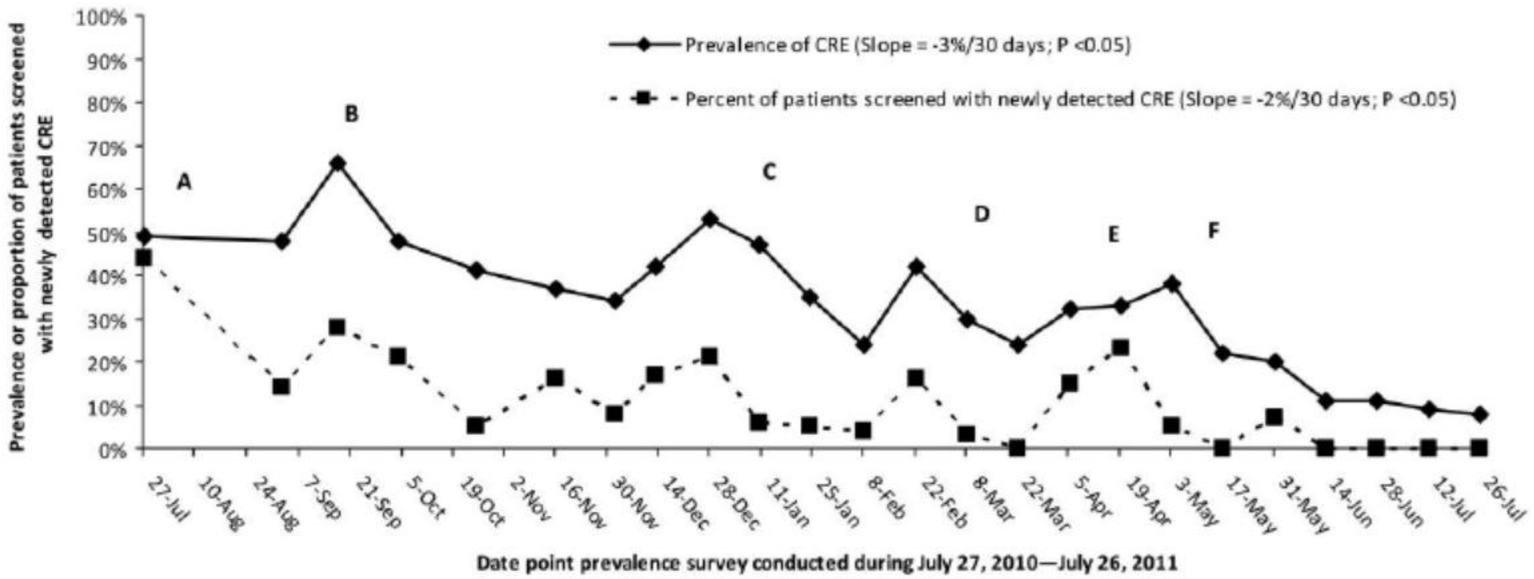
Tacconelli, Lancet Infect Dis, 2009

Mupirocin prophylaxis: high risk patients
Dialysis patients



Tacconelli, Clin Infect D is 2003

Outbreak of Carbapenem-Resistant Enterobacteriaceae at a Long-Term Acute Care Hospital: Sustained Reductions in Transmission through Active Surveillance and Targeted Interventions



Chtnis ICHE 2012

Effect of Daily Chlorhexidine Bathing on Hospital-Acquired Infection

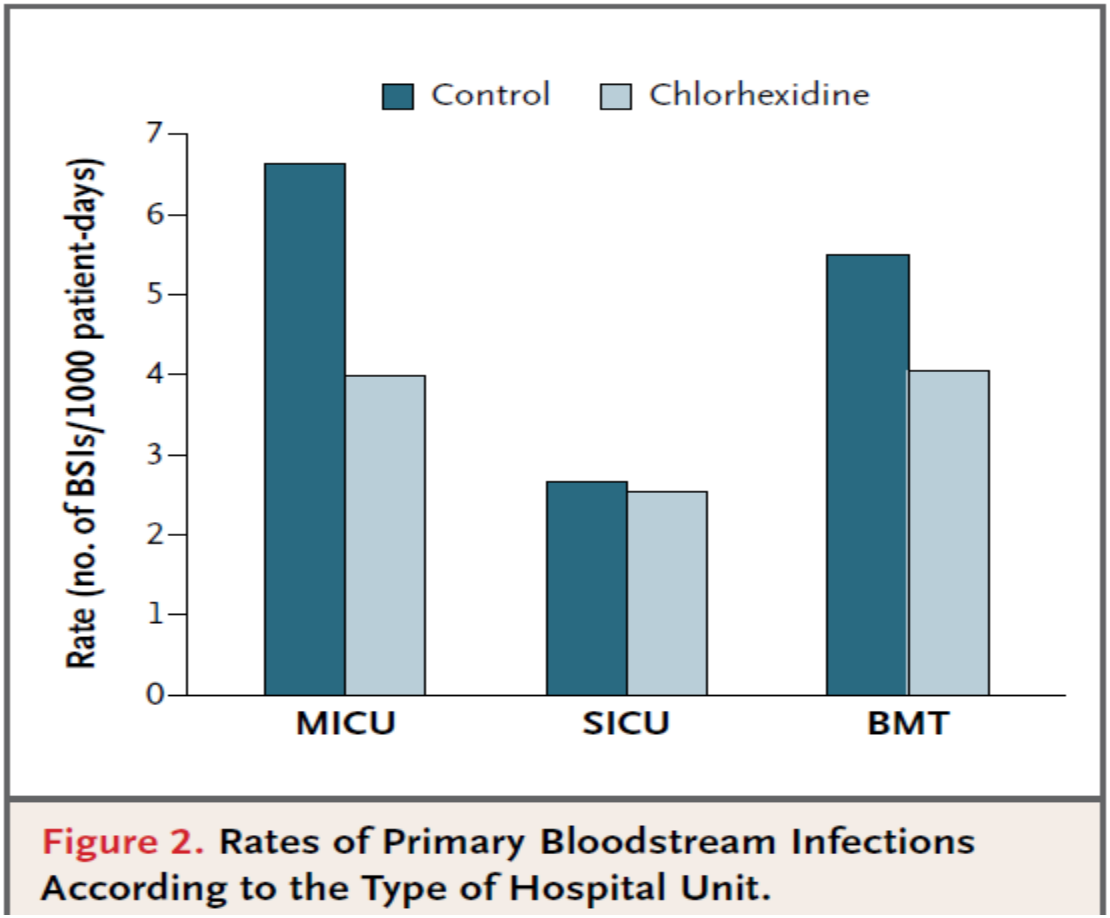


Figure 2. Rates of Primary Bloodstream Infections According to the Type of Hospital Unit.

Climo, NEJM 2013 Feb

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

SHEA The Society for Healthcare Epidemiology of America

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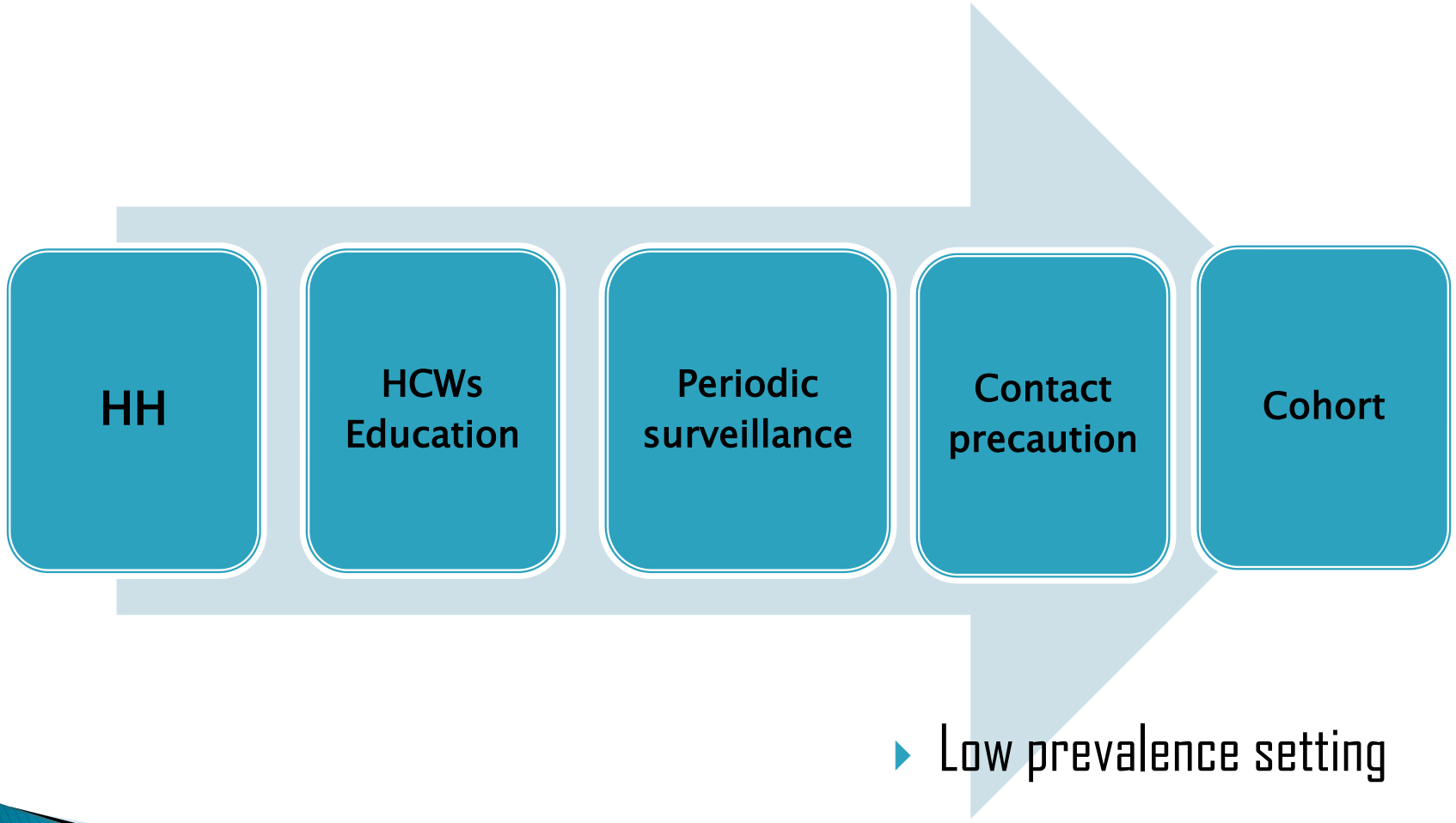
INFECTION CONTROL MEASURES FOR MULTI-DRUG-RESISTANT GRAM-NEGATIVE BACTERIA IN HEALTH-CARE SETTING

Chairperson: Evelina Tacconelli (Tuebingen, IGermany)

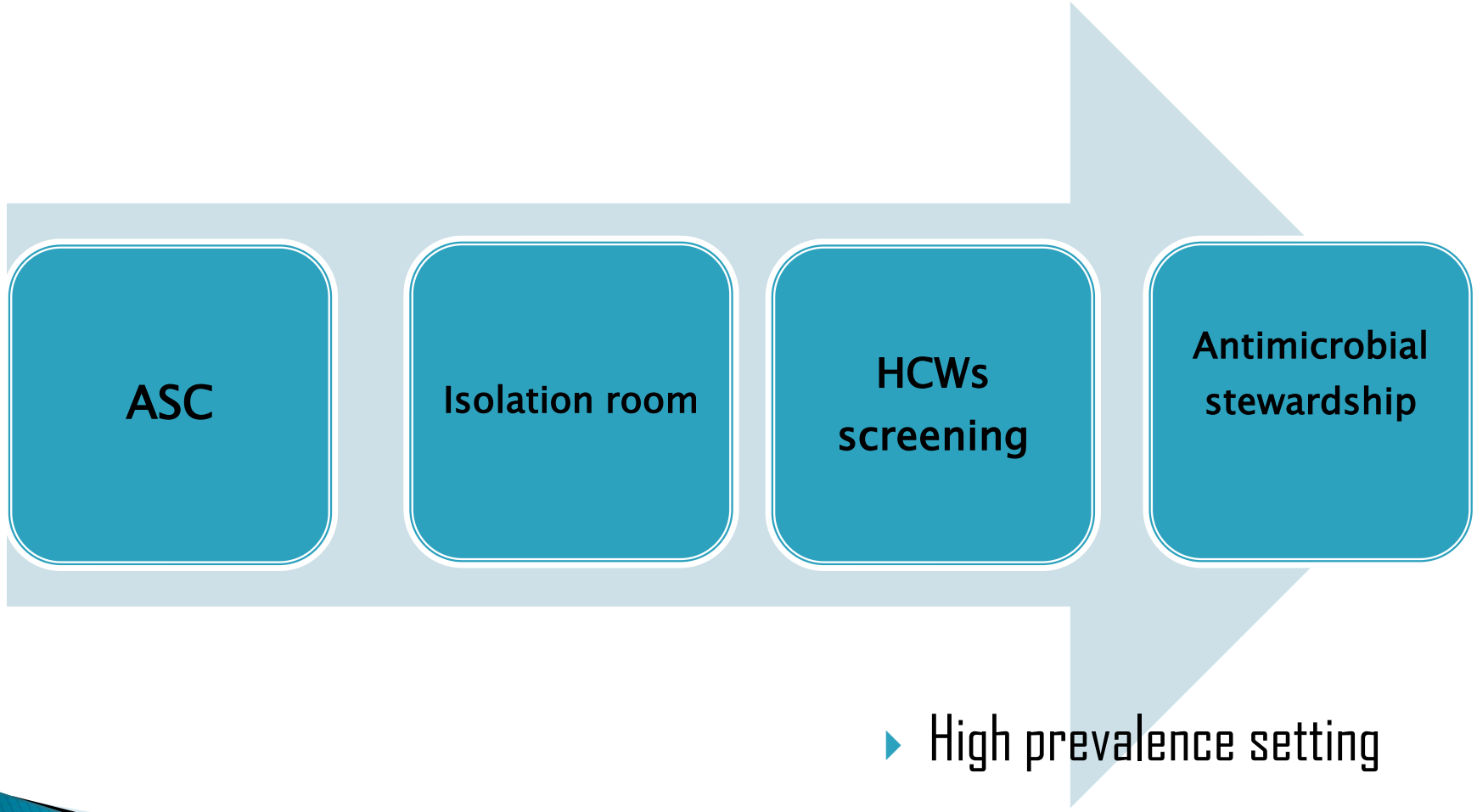
- Yehuda Carmeli (Tel-Aviv University, Tel-Aviv, Israel)
- Barry Cookson (Health Protection Agency, London, UK)
- Stephanie Dancer (Hairmyres Hospital, East Kilbride, Lanarkshire, UK)
- Uwe Frank (Heidelberg University Hospital, Heidelberg, Germany)
- Gunnar Kahlmeter (Central Hospital, Växjö, Sweden)
- Jesus Rodrigues Bano (Hospital Universitario Virgen Macarena, Sevilla, Spain)
- Nalini Singh / Deborak Yokoe (USA)

BASIC PROCEDURE



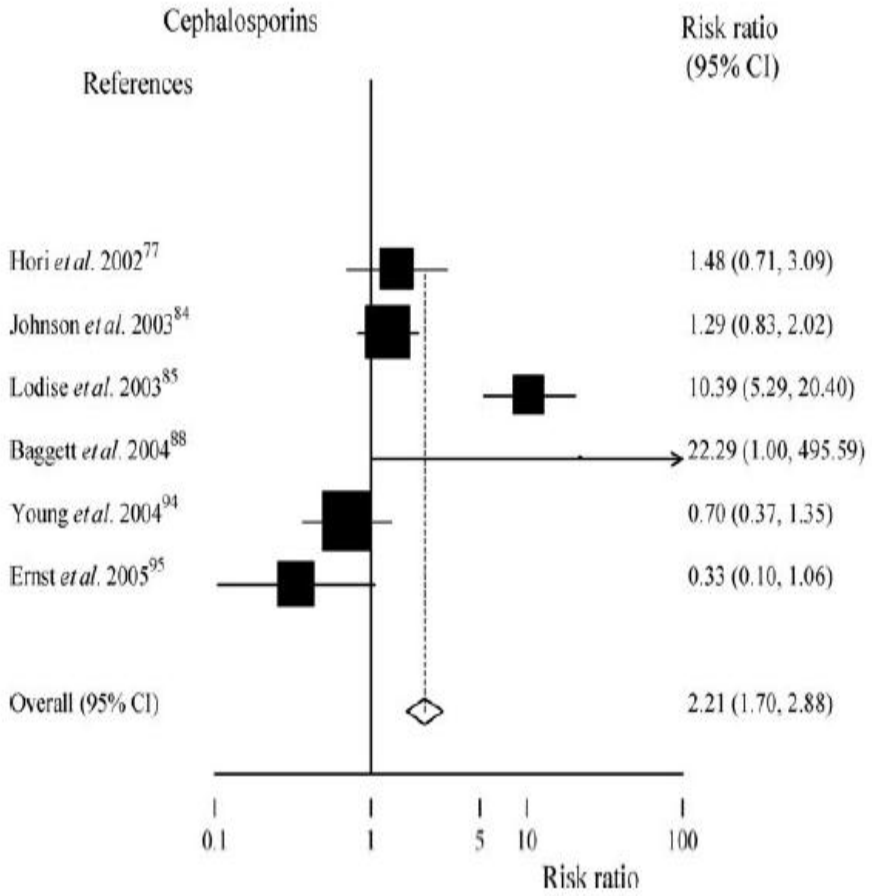
- Low prevalence setting

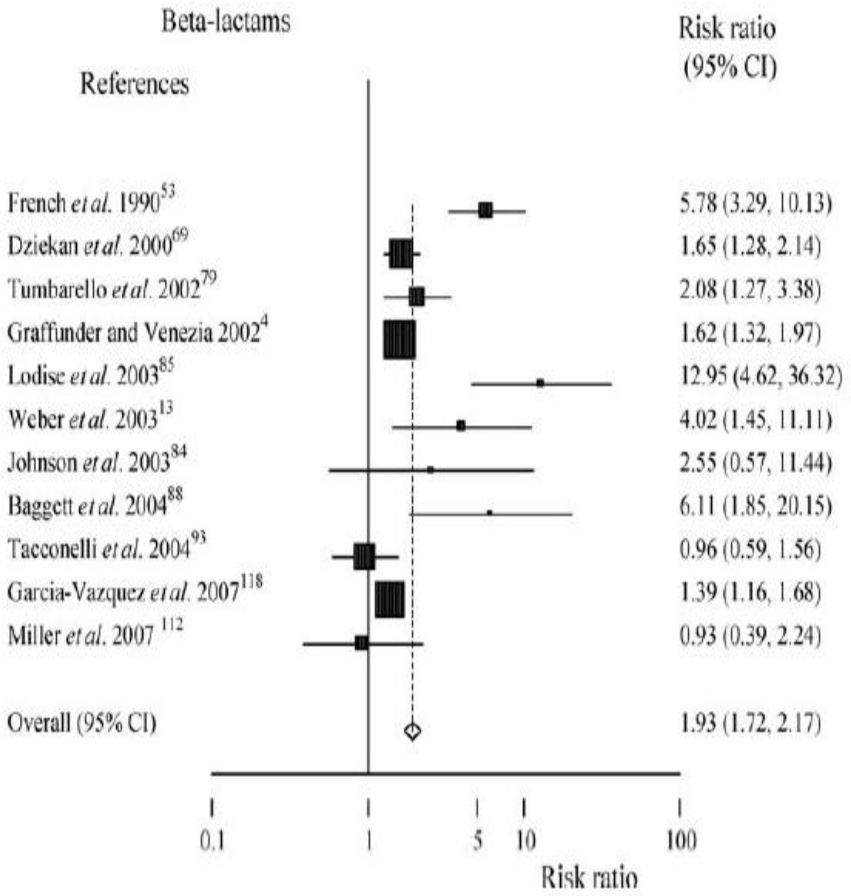
ADDITIONAL PROCEDURES



- High prevalence setting

Systematic review and meta-analysis
Antibiotics and MRSA





Tacconelli, Journal of Antimicrobial Chemotherapy (2008) 61, 26–38

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TABLE 3. Incidence of acquisition for 1,000 antibiotic-days by antibiotic class, patient risk factor, and duration of therapy for the overall target ARB (i.e., MRSA, VRE, and CR-PA) and specific for MRSA

Antibiotic class and risk factor[a]	ARB incidence/1,000 days of antibiotic				MRSA incidence overall
	Overall	By duration of therapy:			
		5 days	10 days	15 days	
Carbapenems	13.8	18.3	13.2	7.6	7.9
Dialysis	29.4				
Diabetes	28.6				
ICU	22.8				
Cirrhosis	20.4				
Broad-spectrum cephalosporins	5.8	5.1	3.5	13.5	2.4
Chronic renal failure	27.3				
Cancer	15.8				
HIV infection	10.9				
Cirrhosis	10.6				
Age of >70 yrs	8.1				
Quinolones	5.9	6.6	5.2	17.2	3.1
Age of >70 yrs	8.3				
Glycopeptides	9.2	11.3	8.0	21.7	3.2
HIV	19.5				
Cirrhosis	15.1				
Macrolides	5.8	7.2	10.9	6.3	8.2
Chronic renal failure	22.7				
Cancer	16.8				
Piperacillin-tazobactam	6.5	11	3.1		3.5
Age of >70 yrs	16.2				

[a] Only relevant risk factors are reported.

Tacconelli, Antimicr Agents Chemoth, 2009

- Interrupted time-series analysis
- Staff education
- IC measures
- Environmental cleaning
- Local guidelines (pocket-size antibiotic guide) on empirical treatment of common infections
- No formal restriction (pharmacist phone call)

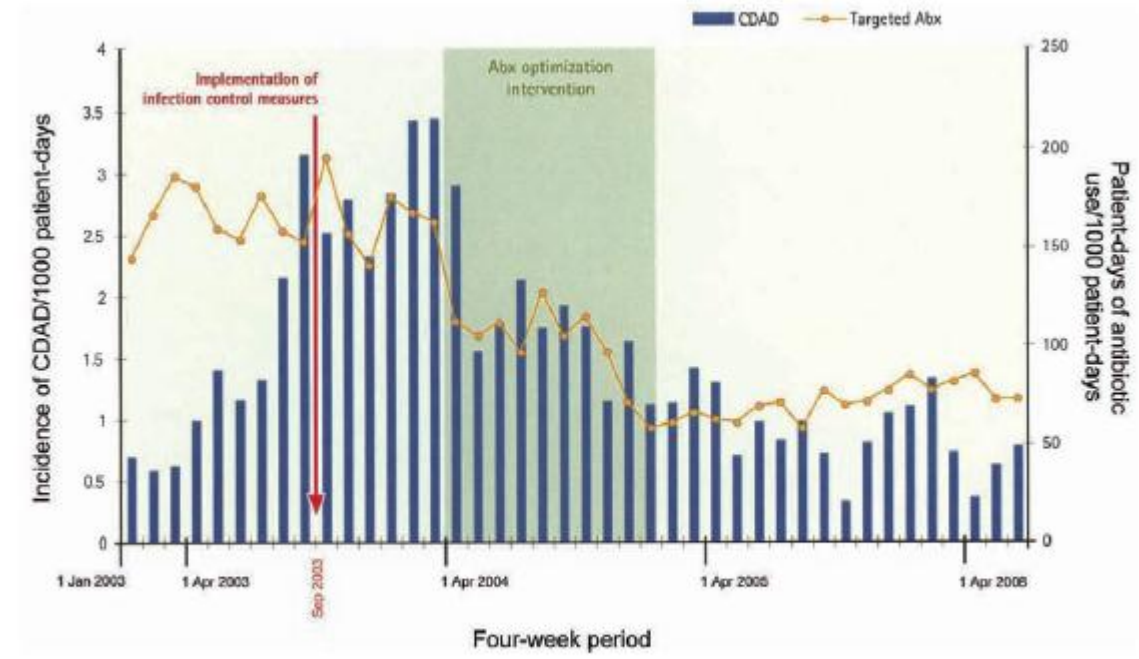


Figure 2. Targeted antibiotic (Abx) consumption and nosocomial *Clostridium difficile*–associated disease (CDAD) incidence per 1000 patient-days of hospitalization.

Valiquette, CID 2007

Table 3.—Change in Number and Incidence of Patient-Related Ceftazidime-Resistant *Klebsiella* From 1995 to 1996 Following Cephalosporin Restriction in 1996*

Site	Year	No. of PR-CRK	Change, %	Incidence by Unpaired Median PR-CRK/ADC Ratio (Range)	*P*	Incidence by Paired Median Monthly PR-CRK/ADC Ratio Difference (Range)	*P*
Hospital-wide	1995	150	−44.0	0.032 (0.015-0.054)	<.01	−0.019 (−0.037-0.014)	<.05
	1996	84		0.019 (0.006-0.039)			
All intensive care units	1995	55	−70.9	0.137 (0.036-0.237)	<.001	−0.098 (−0.237-0.048)	<.01
	1996	16		0.034 (0-0.121)			
Surgical intensive care unit	1995	40	−87.5	0.293 (0.083-0.636)	<.001	−0.194 (−0.636-0.043)	<.005
	1996	5		0 (0-0.143)			
Medical intensive care unit	1995	17	−58.8	0.100 (0-0.300)	>.05	−0.100 (−0.214-0.200)	>.05
	1996	7		0 (0-0.200)			
Cardiac intensive care unit	1995	2	100	0 (0-0.091)	>.05	0 (−0.091-154)	>.05
	1996	4		0 (0-0.231)			

*PR-CRK/ADC indicates number of patient-related ceftazidime-resistant *Klebsiella* (PR-CRK) per 1000 average daily census (ADC), hospital-wide; and per 100 ADC for individual and all intensive care units.

Table 4.—Change in Number and Incidence of Patient-Related Imipenem-Resistant *Pseudomonas aeruginosa* From 1995 to 1996 Following Cephalosporin Restriction in 1996

Site	Year	No. of PR-IRP	Change, %	Incidence by Unpaired Median PR-IRP/ADC* Ratio (Range)	*P*	Incidence by Paired Median Monthly PR-IRP/ADC Ratio Difference (Range)	*P*
Hospital-wide	1995	67	68.7	0.015 (0.003-0.026)	<.01	0.010 (−0.008-0.031)	<.01
	1996	113		0.025 (0.016-0.042)			
All intensive care units	1995	20	75.0	0.032 (0-0.161)	<.05	0.033 (−0.027-0.157)	<.01
	1996	35		0.080 (0.033-0.182)			
Surgical intensive care unit	1995	12	33.3	0.100 (0-0.429)	>.05	0.067 (−0.286-0.250)	>.05
	1996	16		0.143 (0-0.429)			
Medical intensive care unit	1995	8	37.5	0 (0-0.300)	>.05	0.019 (−0.209-0.200)	>.05
	1996	11		0.095 (0-0.200)			
Cardiac intensive care unit	1995	0	. . .	0 (0-0.0)	<.05	0 (0-0.167)	>.05
	1996	7		0 (0-0.167)			

*PR-IRP/ADC indicates number of patient-related imipenem-resistant *P aeruginosa* (PR-IRP) per 1000 average daily census (ADC), hospital-wide and per 100 ADC for individual and all intensive care units

Rahal, JAMA 1998

The pseudo outbreak

- An **abrupt and persistent 30% increase in the rate of nosocomial infections** was detected at a university teaching hospital after a prolonged period with a relatively constant nosocomial infection rate.
- The apparent outbreak began during the same month that an antibiotic stewardship program was started.

Table I Proportion of nosocomial infections reported solely on the basis of a treating physician's diagnosis during the endemic and epidemic periods

Type of nosocomial infection	Proportion of cases reported based on physician's diagnosis alone	
	Endemic period (%)	Epidemic period (%)
Pneumonia	47	57
Urinary tract	17	28
Surgical site	9	15

Table II Attending radiologist's interpretation of chest radiographs obtained among patients reported to have nosocomial pneumonia

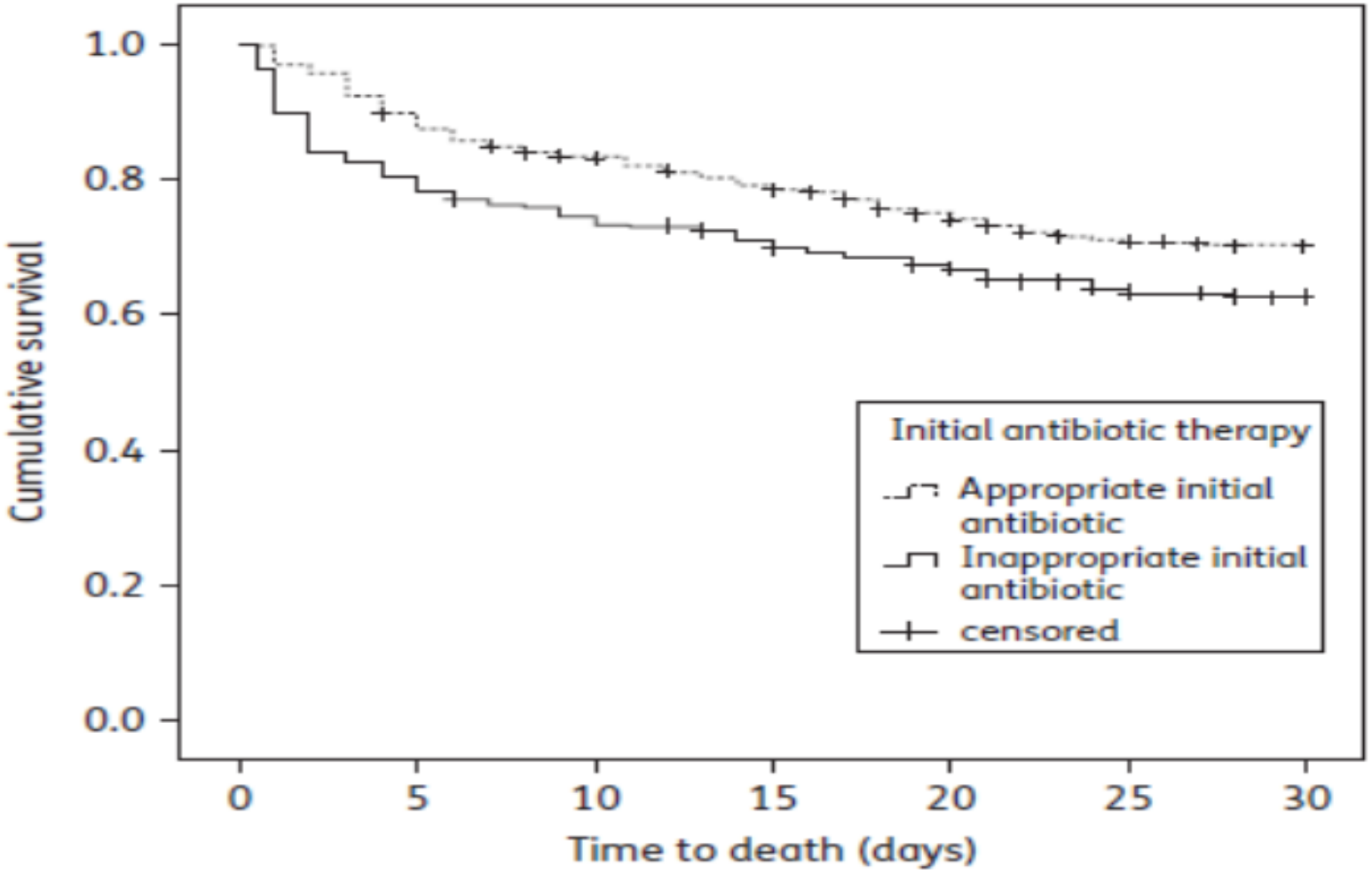
Chest radiograph interpretation	Endemic period ($N = 74$)	Epidemic period ($N = 76$)
Pneumonia	4 (5%) [2]	3 (4%) [1]
Pneumonia in differential diagnosis	12 (16%) [0]	15 (20%) [3]
Diagnosis other than pneumonia	58 (78%) [1]	58 (76%) [4]

$P = 0.80$.

The data are presented as number (percentage). The numbers in brackets indicate the number of reported cases of nosocomial pneumonia among patients in each chest radiograph category. The *P*-value corresponds to the proportion of radiographs in the two periods in which pneumonia was either definitely present or in the differential diagnosis (according to radiologist).

Calfee, J hosp infect 2003

Predictive factors for early mortality among patients with methicillin-resistant Staphylococcus aureus bacteraemia



Gasch, JAC Feb 2013

MRSA BSI at hospital admission

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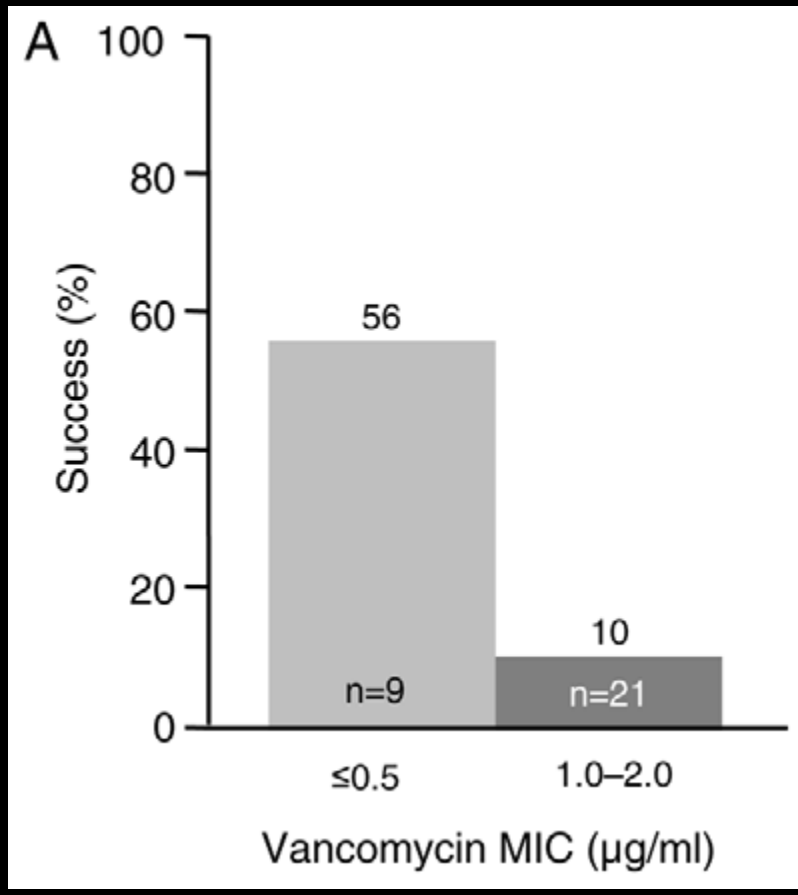
Table 3.. Two logistic regression analyses of risk factors associated with healthcare-associated MRSA bacteraemia within 24 h of hospitalization, including (first model) and excluding (second model) a history of previous MRSA infection o

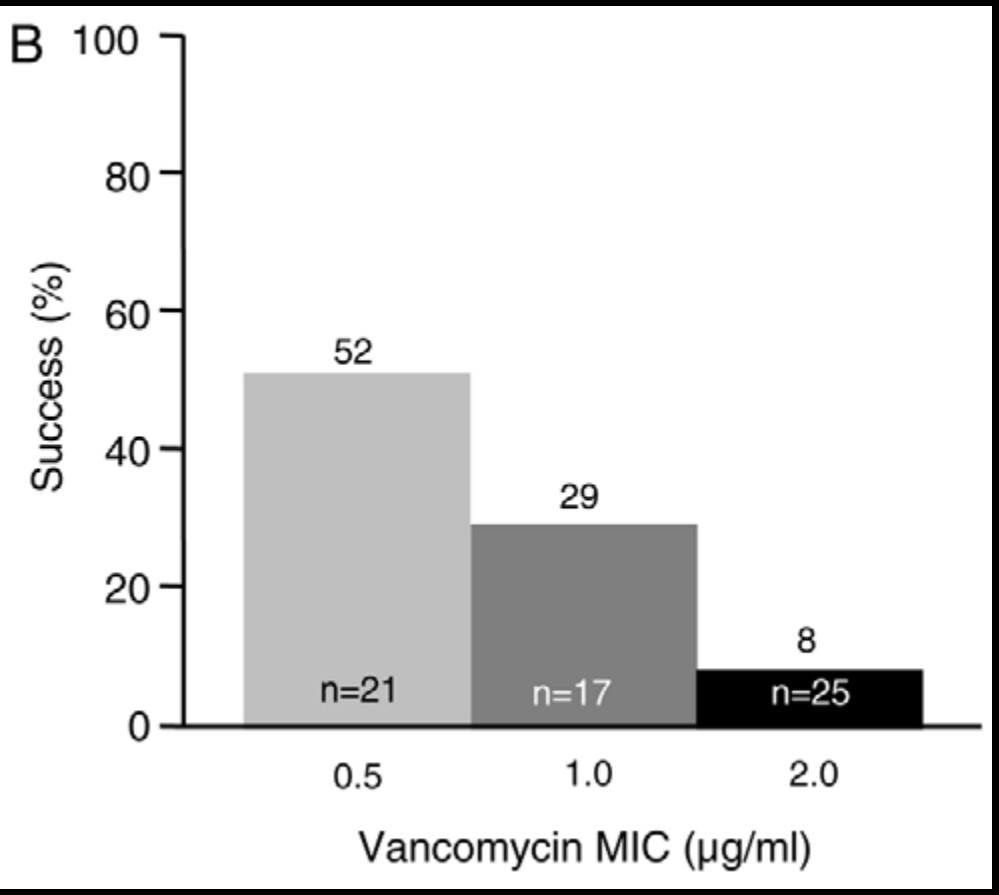
Variables	OR	95%CI	*P* value
First model			
previous MRSA infection or colonization	17.04	4.98–58.27	<0.001
cellulitis at hospital admission	4.27	1.52–11.94	0.006
presence of a central venous catheter	3.30	1.71–6.38	<0.001
skin ulcers at hospital admission	3.12	1.37–7.11	0.007
Second model			
presence of a central venous catheter	3.24	1.76–5.97	<0.001
hospitalization in the previous 6 months	2.01	1.11–3.65	0.02
quinolone therapy in the previous 30 days	1.99	1.07–3.69	0.02
diabetes mellitus	1.84	1.05–3.22	0.03

Tacconelli E, JAC, 2004

Vancomycin, MIC and mortality



Sakoulas et al. J Clin Microb 2004



Moise-Broder et al. CID 2004

Gould I. Int J Ant Ag 2008

MRSA BSI
UK online survey

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108 respondents

- 42% vancomycin alone (removable focus infections)
- 49% plus RFD (cardiac / orthopaedic origin)
- 69% linezolid as a second-line agent
- 19% daptomycin

Table 1. Percentage of positive responses to choice of antimicrobial based on vancomycin MIC (mg/L)

	MIC (mg/L)			
Action	1	2	4	>4
Continue unchanged	83.3	50	0	0
Add in rifampicin	88.9	61.1	25	2.8
Add in an aminoglycoside	50	66.7	33	16.7
Change to daptomycin	25	18.8	50	81.3
Change to linezolid	29	38.2	76.5	91.2
Change to tigecycline	75	25	25	50

Hussain JAC 2010

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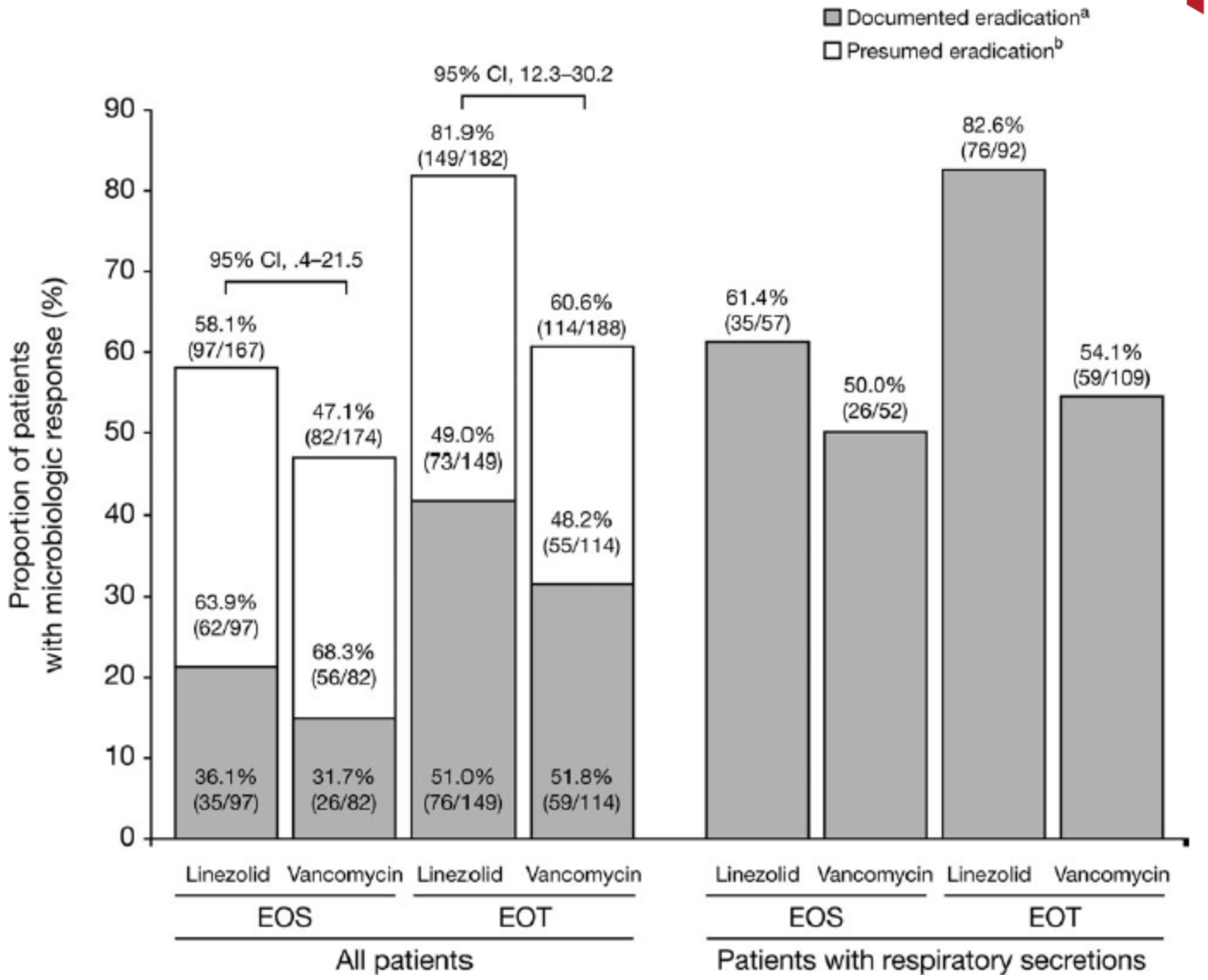
Asking the Right Clinical Question
Linezolid versus Vancomycin

Disease	Journal / Year	Results
BSI Gram+	LID / 2008 IJAA / 2010	L > V L = V
BSI S. aureus	JAC / 2005	L = V
Pneumonia Gram +	LID / 2008 IJAA / 2010	L = V L = V
Pneumonia MRSA	CCM / 2010	L = V
SSI Gram +	LID / 2008 IJAA / 2010	L > V L > V
SSI MRSA	AJS / 2009 CRMS / 2010 CRMS / 2010 [2]	L = V L = V L > V

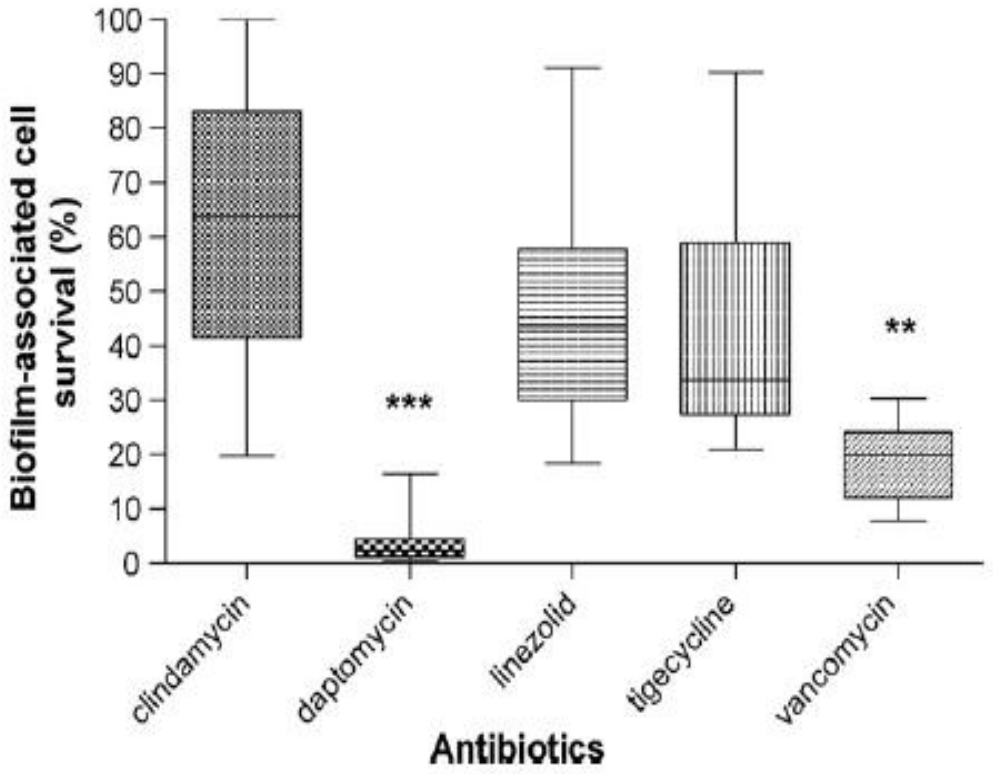


Wunderink, CID 2012

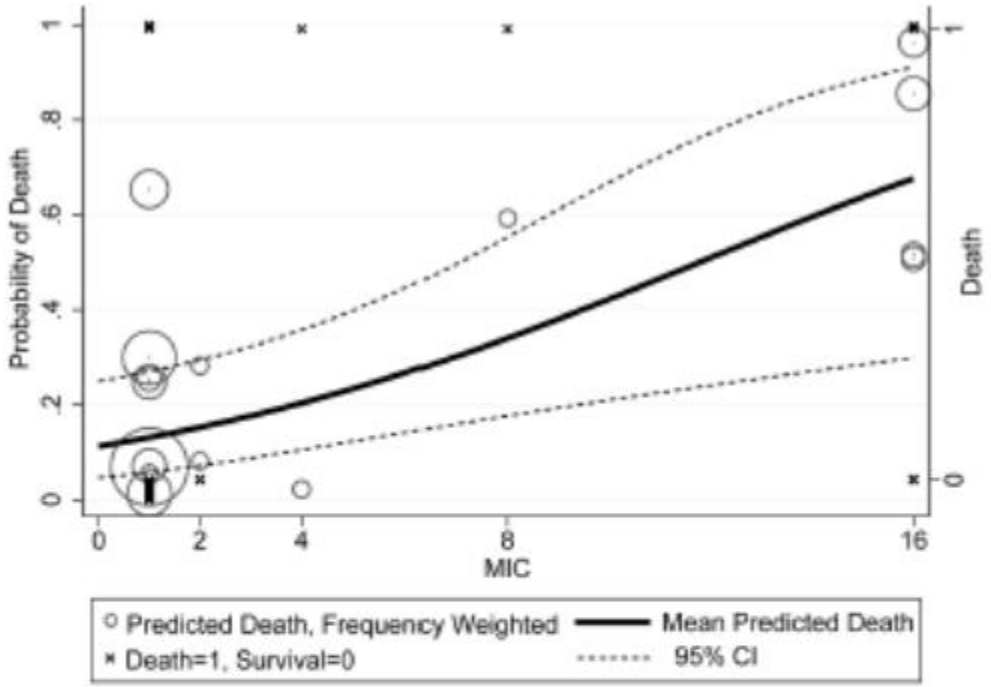
Criticisms

- Unequal distribution of medical comorbidities
- Clinical cure was a subjective outcome ("resolution of clinical signs and symptoms of pneumonia compared with baseline, improvement or lack of progression in chest imaging, and no requirement for additional antibacterial treatment")
- Majority of HAP are not diagnosed
- Lack of loading dose for vancomycin

New drugs and biofilm MRSA



Smith, Intern J Antimicrobiol Agents, 2008



MIC (mg/L)	Unadjusted Actual Values Died (n,%)	Sensitivity for a cutpoint equal to or greater than the MIC	Specificity for a cutpoint equal to or greater than the MIC
1	9/54, 16.7%	100%	0%
2	0/2, 0%	52.6%	90%
4	1/1, 100%	52.6%	94%
8	1/1, 100%	47.4%	94%
16	8/11, 72.7%	42.1%	94%

Esterly, JAC 2012

The case of colistin

- According to a non-randomised trial, colistin was less effective and safe than betalactams in different infections caused by MDR-GNB
  - Groups were not comparable
    - patients in the colistin group were elders,
    - coming from healthcare facilities
    - with ventilator-associated support
    - receiving inappropriate empiric treatment
- In contrast, other non-randomised studies concluded that colistin has similar efficacy and security compared to betalactams
- In a systematic review on KPC, monotherapy with polymyxins was associated with poor response rates, whereas combination therapy gave more promising results

Paul, JAC 2010; Falagas, IJAA 2010; Kallel, Int Care Med 2007; Hirsch and Tam, JAC 2010

The case of fosfomycin

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- In vitro activity against MDR Enterobacteriaceae, including a high proportion of P. aeruginosa
- Clinical experience is lacking
- The activity of fosfomycin was evaluated against 68 KPC-producing *K pneumoniae* isolates, 23 of which were nonsusceptible to tigecycline and/or colistin.
- The susceptibility rates were 93% for the overall group
  - 87% for the group nonsusceptible to tigecycline and/or colistin
  - 83% for the extremely drugresistant subgroup that was nonsusceptible to tigecycline and/or colistin.
- Clinical correlation of this in vitro study is needed

Endimiani, AAC 2010

The case of tygecicline

- Clinical experience with carbapenem-resistant strains is limited
- A recent review gathered data from 15 publications on the treatment of 55 patients with KPC-related infections. A favorable outcome was achieved in 5 of 7 patients treated with tigecycline
- Clinical failures have been reported
- Primary BSI and UTI present a challenge for the use of tigecycline

Hirsch, JAC 2010; Anthony, CID 2008

What is the evidence for the treatment of infections due to MDR-GN?

The case of tygecicline

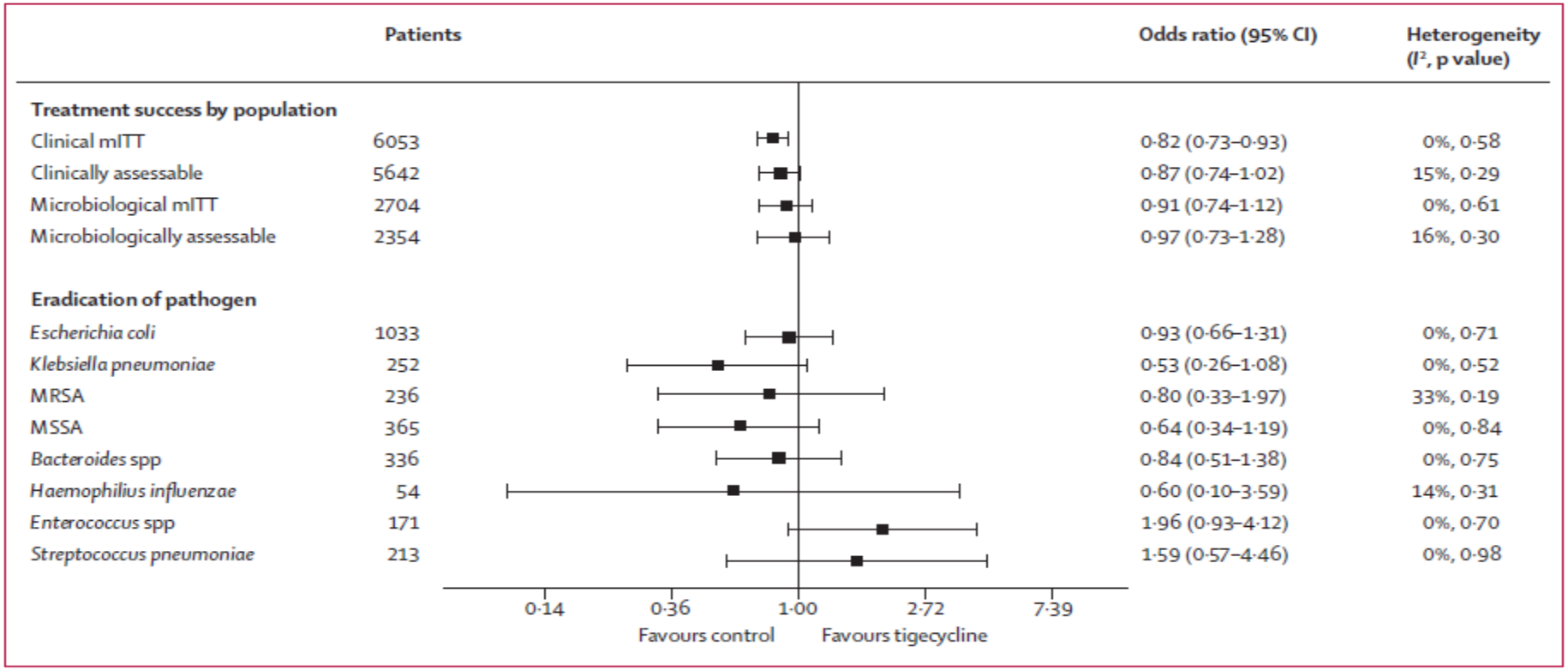

***Figure 4*: Comparative effectiveness of tigecycline versus comparator antibiotics**
Vertical line indicates no difference between the two treatment groups. Pooled odds ratios were calculated from random-effects models with the Mantel-Haenszel method. mITT=modified intention to treat. MRSA=meticillin-resistant *Staphylococcus aureus*. MSSA=meticillin-sensitive *Staphylococcus aureus*.

All cause mortality was higher in the tygecicline group than in the comparator, but the difference was not statistically significant (1.28, 0.97 – 1,69)

Tasina, LID 2012

The case of KPC infections

- Clinical data on the treatment of KPC infections are very limited and consist mainly of small case series and brief reports.
- A total of 15 studies/reports containing 55 unique patient cases
- Treatment with:
  - Aminoglycosides 75%, Polymyxin combinations 73%
  - Tigecycline 71%

  appeared to have higher success rates

  In contrast:
  - Carbapenem 40%, Polymyxin 14% monotherapy

  had much lower associated success rates

Hirsch, JAC 2010

Is there any efficacy data for the combination therapy?

- Carbapenems are occasionally used in combination with colistin
- The rationales include
  - low level resistance to carbapenems
  - reports on inhibitory effects of carbapenem in-vitro despite increased MICs
  - synergism studies
  - lack of other effective treatments.
- Some in-vitro studies indicate synergism between colistin and carbapenems for colistin-susceptible- carbapenem resistant

Is there any efficacy data for the combination therapy?

- In a more recent study, the checkerboard technique was used to test for synergistic activity of various combinations of anti-pseudomonal agents
  - ceftazidime-tobramycin,
  - piperacillin-tazobactam-tobramycin
  - imipenem-tobramycin
  - imipenem-isepamycin
  - imipenem-ciprofloxacin
  - ciprofloxacin-tobramycin
- Ceftazidime-tobramycin and piperacillin-tazobactam-tobramycin combinations were associated with the highest ratios of synergy
- Antagonism was not observed in any of the combinations

Dundar, Yonsei Med J 2010

Is there any efficacy data for the combination therapy? Rifampicin

- Data in the literature on combined therapeutic regimens with rifampicin are limited and refer mostly to uncontrolled studies
- The real clinical benefit of using rifampicin-containing therapies for the treatment of MDR-GN bacteria in terms of clinical outcome and survival rates still needs to be assessed

Drapeau, Int J Antim Ag, 2010