Do gram positive infections still pose a major threat to patients and health care system?

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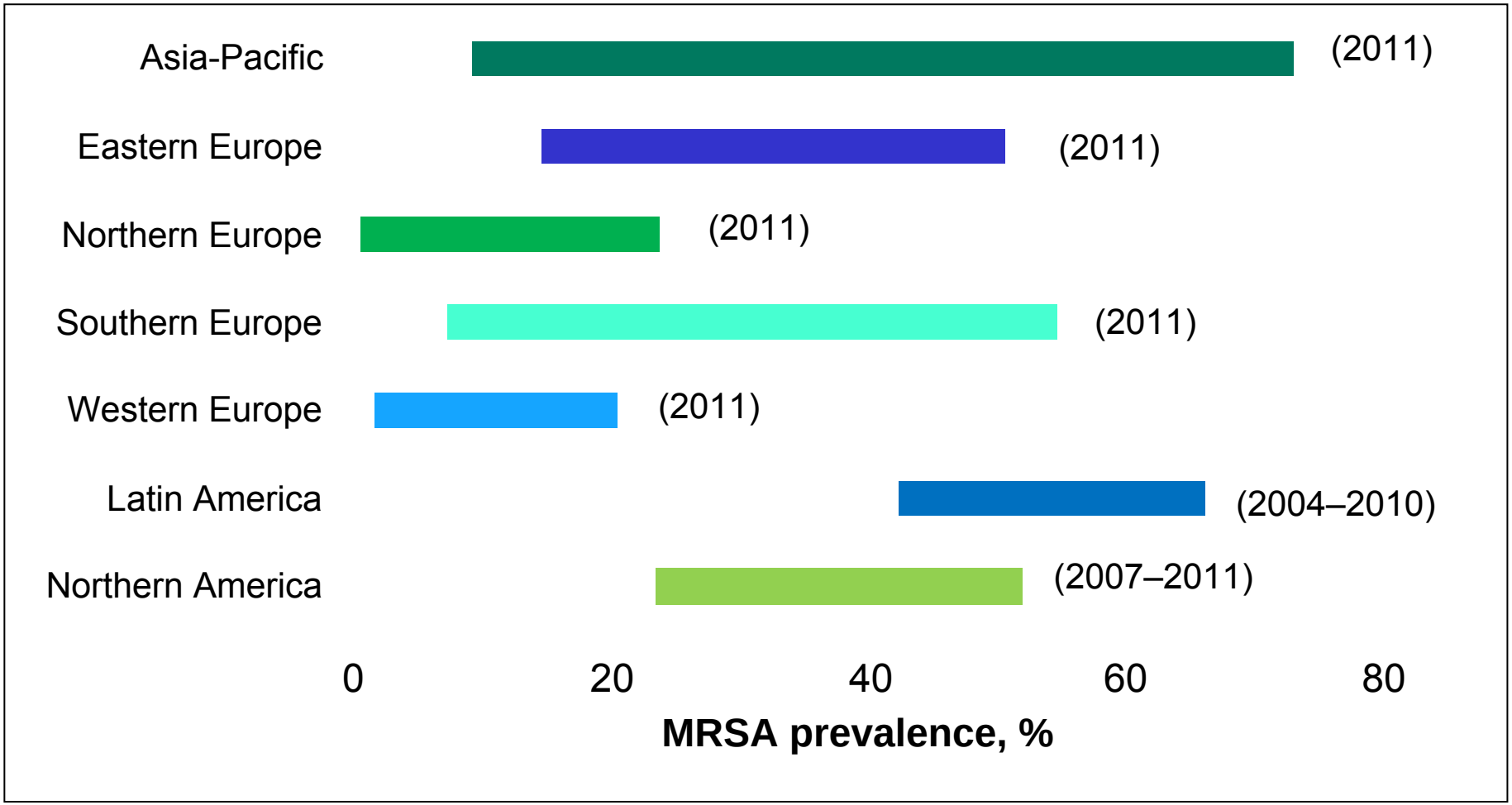
  - Astellas
  - AstraZeneca
  - Bayer Healthcare
  - Cubist
  - Durata
  - MSD
  - Novartis
  - Pfizer

Gram-positive resistant pathogens
MRSA prevalence by geographical region

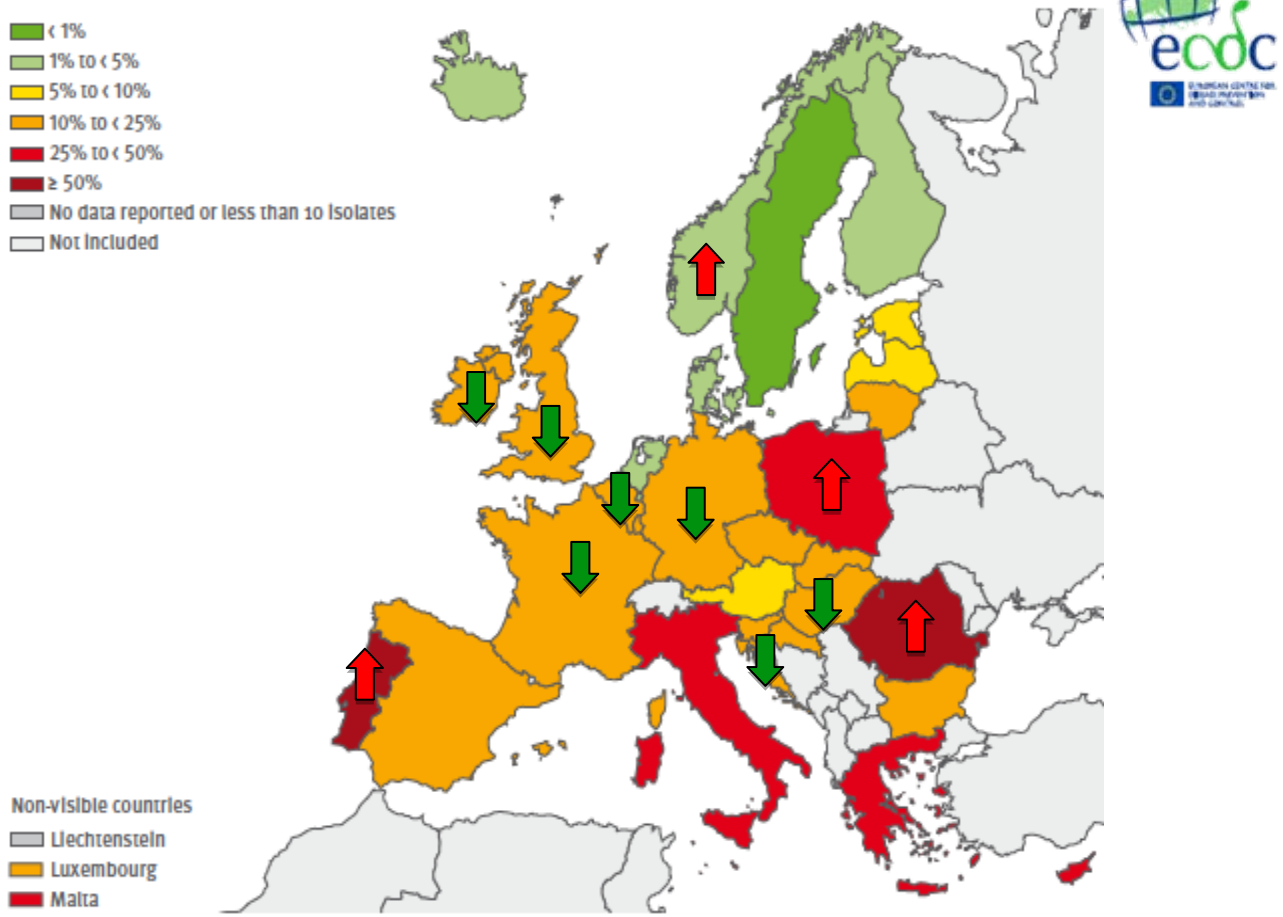


MRSA, methicillin-resistant *Staphylococcus aureus*

Dryden… Eckmann et al. *Clin Microbiol Infect*. 2015 [ePub ahead of print].

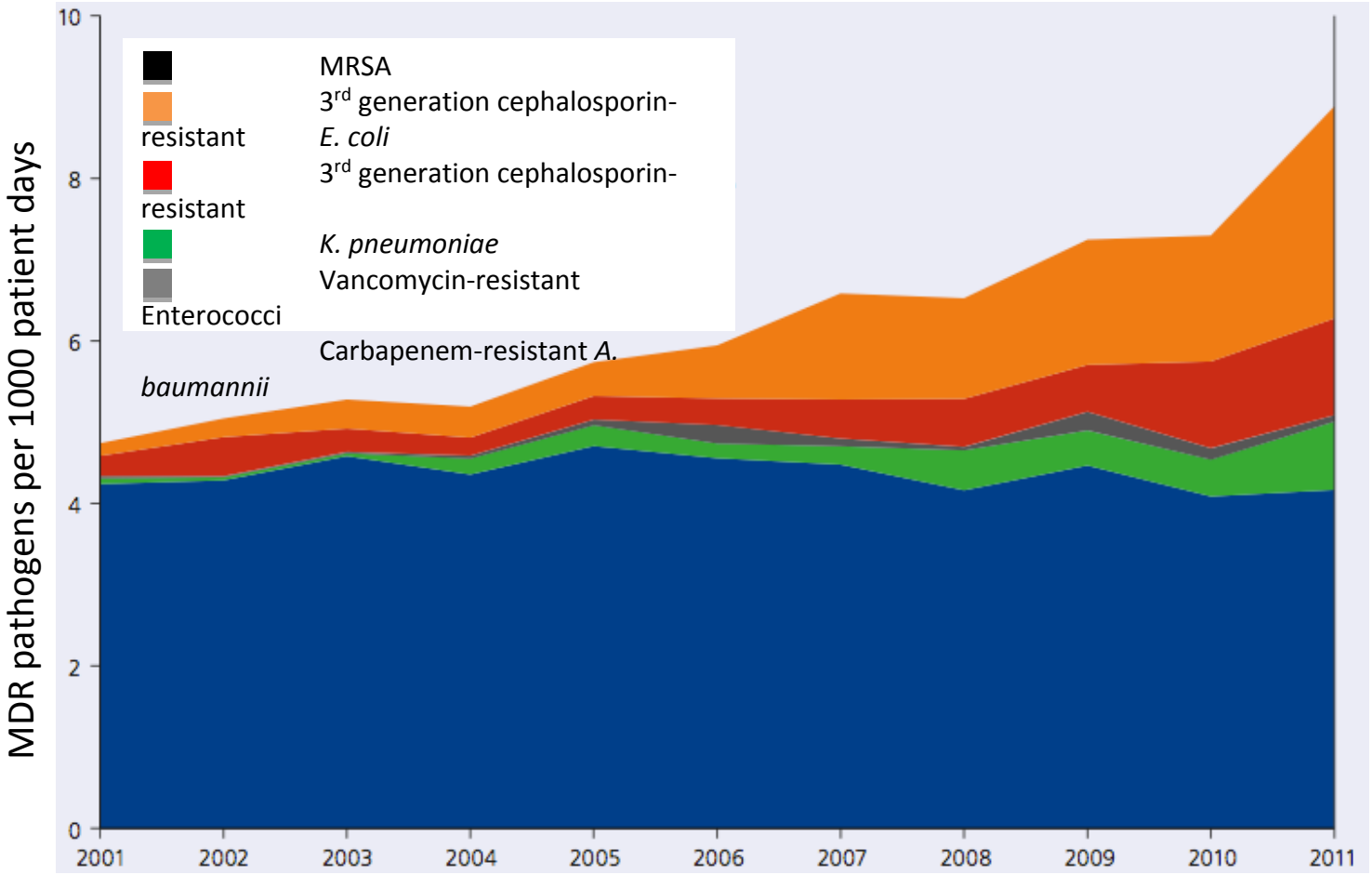
Although falling in some areas MRSA continues to be a problem

Trends in Europe from 2011 to 2012[2]



1. Dantes R. *et al. JAMA Intern Med*. 2013;173(21):1970–1978.
2. EARS-NET report 2012. Available at http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx. [Accessed November 2013].

Antimicrobial resistance in Germany: Overview of incidence density in ICU



MRSA, methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit; MDR, multidrug resistant.

Adapted from GERMAP 2012. Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin in Deutschland. Antiinfectives Intelligence, Rheinbach, 2014. Available at: www.p-e-g.org/econtext/germap [Accessed December 2014]

Hospital mortality rates in critically ill patients with *S. aureus*

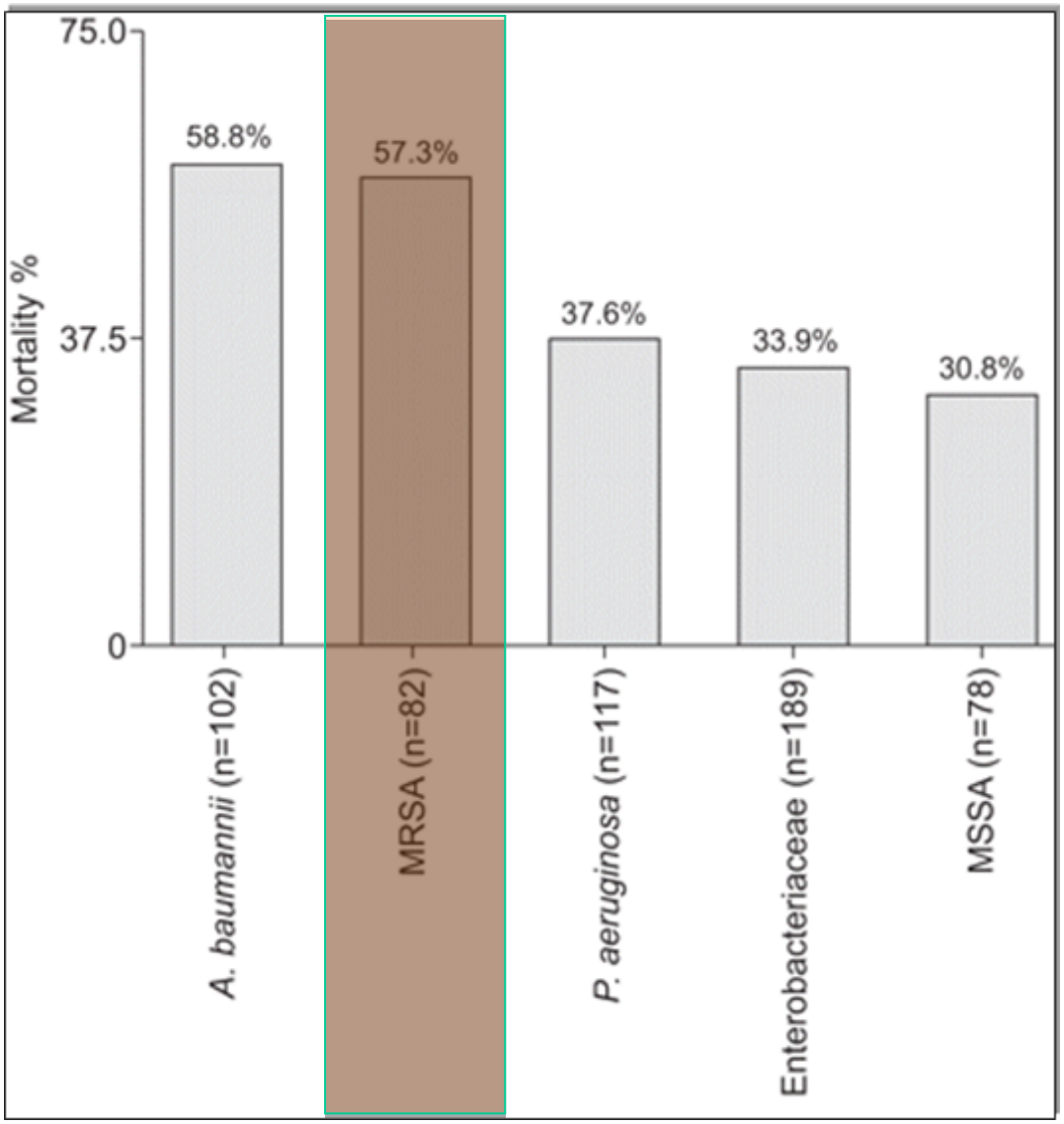
- Mortality rate (MRSA vs MSSA)
- ICU: 29.1% vs 20.5% (*P*<.01)
- Hospital: 36.4% vs 27.0% (*P*<.01)
- Adjusted OR 1.46 (*P*=.03)

MRSA is independently associated with higher hospital mortality rates amongst critically ill patients with *S. aureus* infections

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*

Hanberger et al. *Int J Antimicrob Agents* 2011;38(4):331–335.

Mortality according to bacterial aetiology



MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*
Rello et al. *Eur Respir J*. 2011;37:1332–9.

ESCAPE Pathogens

Clinical Outcomes: Mortality

	VRE	VSE	
Bacteremia[1]	n=683	n=931	OR 2.52*
	MRSA	MSSA	
Bacteremia[2]	11.8% (n=382)	5.1% (n=433)	p<0.001
	KPN-ESBL+	KPN-ESBL-	
Bacteremia[3]	52% (n=48)	29% (n=99)	p<0.05
	AB (IMP-R)	AB (IMP-S)	
Bacteremia[4]	57.5% (n=40)	27.5% (n=40)	p=0.007
	MDR-Pae	No-MDR-Pae	
Bacteriemia[5]	21% (n=40)	12% (n=40)	p=0.08
	EB (IMP-R)	EB (IMP-S)	
Serious infections[6]	33% (n=33)	9% (n=33)	p=0.038

vancomycin-resistant enterococci
VSE=vancomycin-susceptible enterococci
MRSA=methicillin-resistant *S.aureus*
MSSA=methicillin-susceptible *S.aureus*
KPN=*K.pneumoniae*
ESBL=extended-spectrum β-lactamase
AB=*A.baumannii*
IMP=imipenem
Pae=*P.aeruginosa*
EB=*Enterobacter spp.*

1. DiazGranados et al. *Clin Infect Dis.* 2005; 41:327–33.
2. Melzer M, et al. *Clin Infect Dis.* 2003;37:1453-1460.
3. Tumbarello M, et al. *Antimicrob Agents Chemother.* 2006;50:498-504.
4. Kwon K. et al. *J Antimicrob Chemother.* 2007;59:525–530.
5. Aloush V. et al. *Antimicrob Agents Chemother.* 2006;50: 43–48.
6. Marchaim D. et al. *Antimicrob Agents Chemother.* 2008; 52:1413-1418.

Economic burden of MRSA infection – USA /Canada

- On average, hospital stays for MRSA infections cost $14,000, compared with $7,600 for all other stays,
- The length of hospitalization was more than double=10.0 days for MRSA infections versus 4.6 days for all other stays.
- A single CA-MRSA case costs third-party payers $2,277 – $3,200
- and society $7,070 – $20,489, depending on patient age (productivity losses)
- Additional LOS and costs estimated to be:

  17 days and $25,819 per infected patient (Canada)

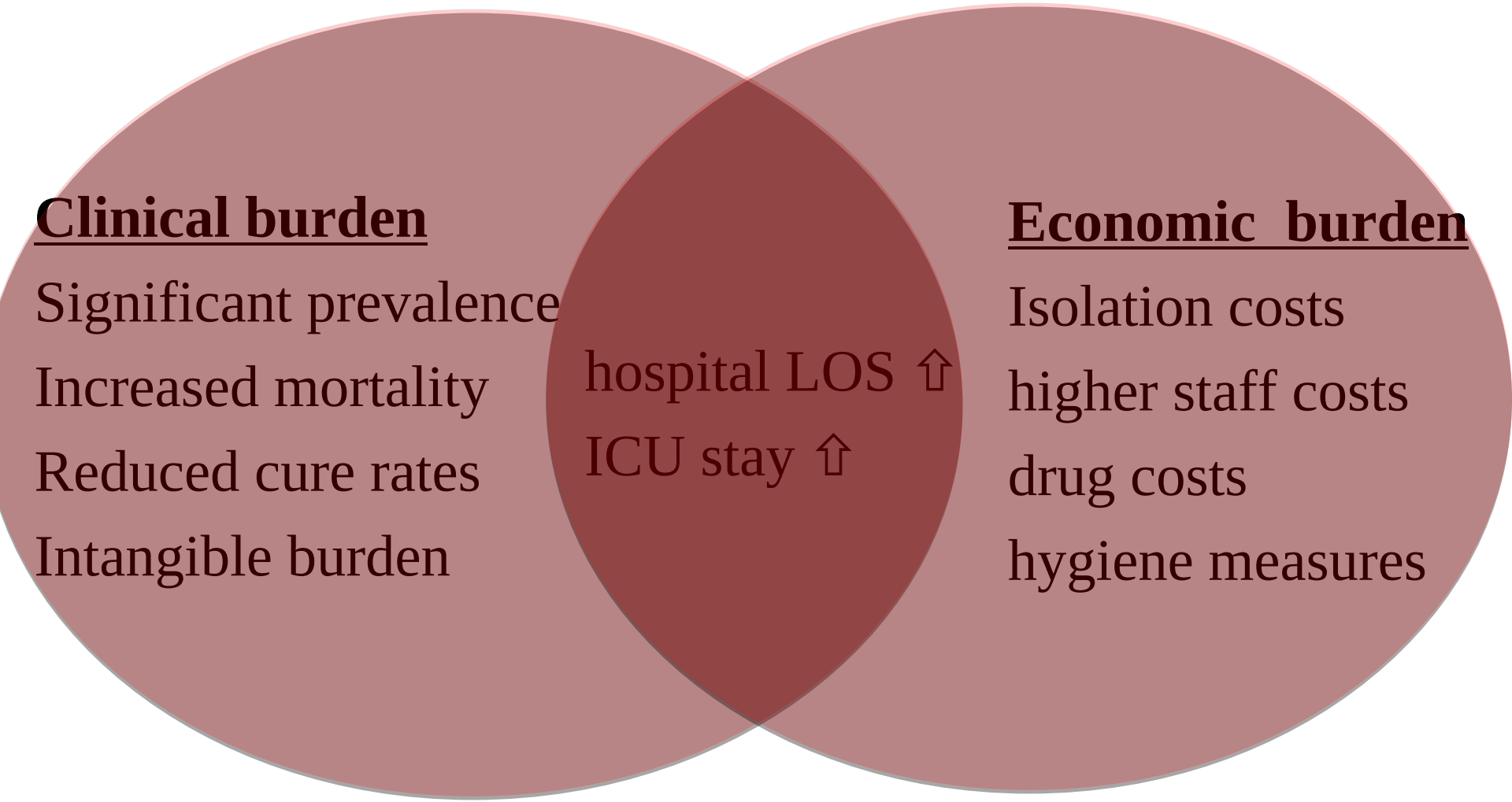
Elixhauser A et al.. Healthcare **Cost** and Utilization Project (HCUP) Statistical Briefs [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006 Feb-.2007 Jul.
Lee BY et al Clin Microbiol Infect. 2013 Jun;19(6):528-36.
Roth VR et al. PLoS One. 2016 Jul 27;11(7):e0159667.

MRSA-attributed costs in Germany

- The mean length of hospital stay was 23 days and the mean time in isolation was 17 days
- MRSA-attributable costs were €8,673 per patient

Hübner C et al. . Eur J Clin Microbiol Infect Dis. 2014 Oct;33(10):1817-22.

Clinical and economic burden of MRSA



The cost-efficiency strategy in the setting of high fixed costs

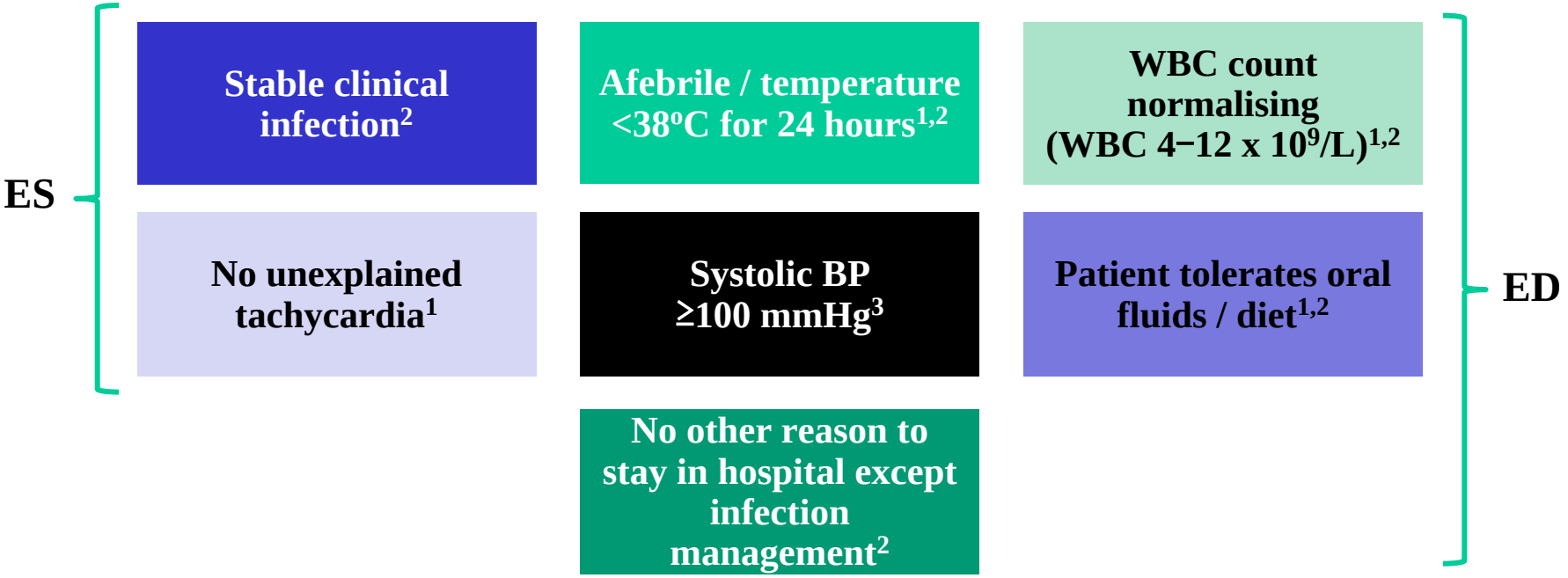
- **Therefore, shortening LOS can be a key efficiency driver[1]**

DRG, diagnosis-related group; LOS, length of stay.

ard WJ, et al. *Healthc Financ Manage*. 2006;60:92−98; 2. Nathwani D. *J Infect*. 2009;59:S40−S50.

ES/ED criteria

- Literature review with expert validation formed the basis for a list of 14 criteria tested in the study; inclusive of Desai[1] and Parodi[2] criteria
- The key (essential) criteria were selected by KOLs, and were used to estimate ES/ED hypothetical opportunities



ED, early discharge; ES, early switch; WBC, white blood cell.

1. Desai M, et al. *BMC Infect Dis* 2006;6:94; 2. Parodi S, et al. *J Manag Care Pharm* 2003;9:317−26; 3. Nathwani D, et al. Clin Microbiol Infect. ;20:993– 1000.

Pan-European early switch/early discharge opportunities exist for hospitalized patients with methicillin-resistant *Staphylococcus aureus* complicated skin and soft tissue infections

D. Nathwani[1], C. Eckmann[2], W. Lawson[3], J. M. Stephens[4], C. Macahilig[5], C. T. Solem[4], D. Simoneau[6], R. Chambers[7], J. Z. Li[8] and S. Haider[9]

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journal homepage: http://www.elsevier.com/locate/ijantimicag

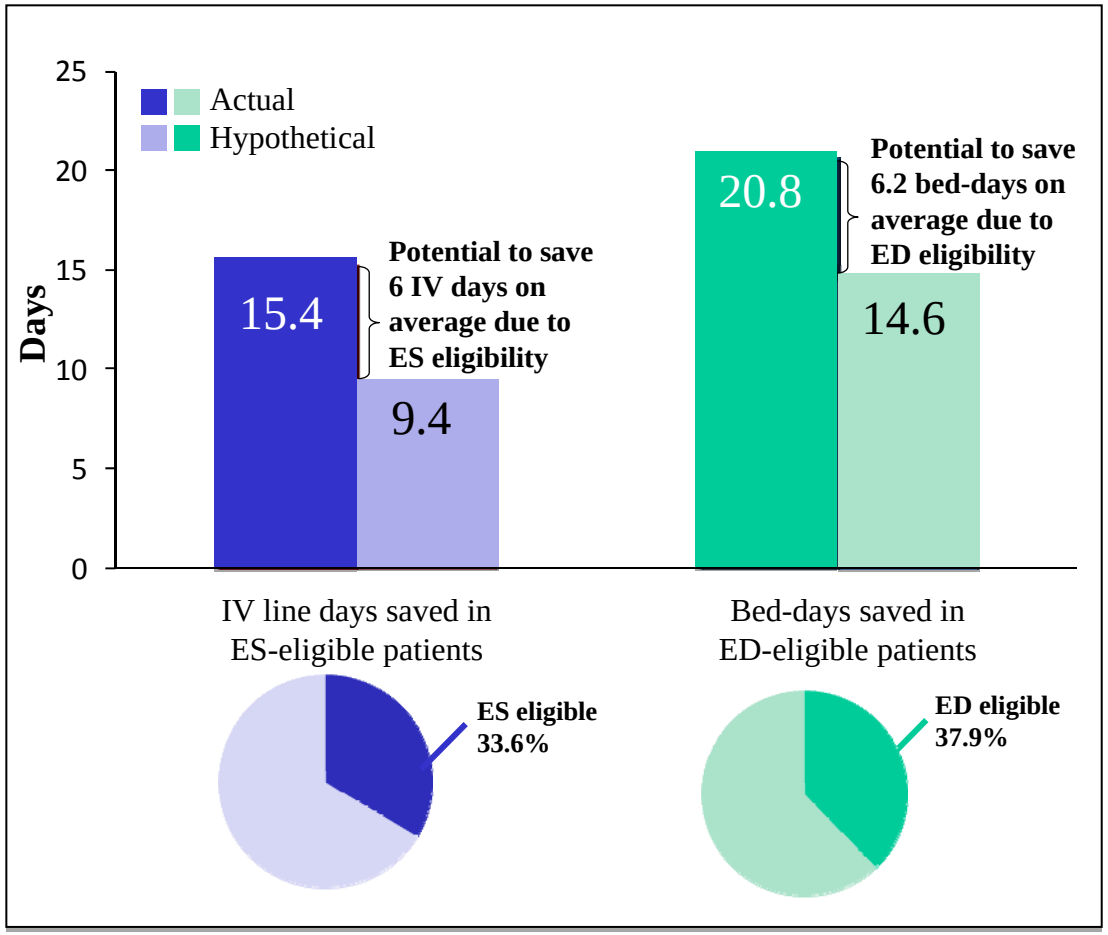
Antibiotic treatment patterns across Europe in patients with complicated skin and soft-tissue infections due to meticillin-resistant *Staphylococcus aureus*: A plea for implementation of early switch and early discharge criteria

Christian Eckmann[a], Wendy Lawson[b], Dilip Nathwani[c], Caitlyn T. Solem[d], Jennifer M. Stephens[d,*], Cynthia Macahilig[e], Damien Simoneau[f], Petr Hajek[g], Claudie Charbonneau[f], Richard Chambers[h], Jim Z. Li[i], Seema Haider[j]

ıthwani D, et al. *Clin Microbiol Infect*. 2014;20:993–1000; 2. Eckmann C et al. *Int J Antimicrob Agents*. 2014;44:56–64.

Key results: ES/ED

- 33.6% of patients were ES eligible ⇒
  - Potential average savings of 6 IV line days in those patients
- 37.9% of patients were ED eligible ⇒
  - Potential average savings of 6.2 bed-days in those patients
- On average >€2000 per ED eligible patient could be saved in bed-day costs (assuming €345 per bed-day)



ED, early discharge; ES, early switch

wani D, et al. *Clin Microbiol Infect*. 2014;20:993–1000. Eckmann C et al. *Int J Antimicrob Agents*. 2014;44:56–64

ES and ED opportunities in hospitalised patients with MRSA cSSTI: Potential savings

- "On the assumption of an average cost of €345 per bed-day, the total savings for the randomly selected population would be over €1.2 million, with more than €2000 in bed-day cost savings being realised per ED-eligible patient"

cSSTI, complicated skin and soft tissue infection; ED, early discharge; ES, early switch; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*

Nathwani D, et al. Clin Microbiol Infect 2014;20:993–1000.
Eckmann C, et al. Int J Antimicrob Agents 2014;44:56–64.

EU.TYG.2014.030 Date of preparation August 2014

Tedizolid versus linezolid for the treatment of ABSSSI

- Phase III, multinational, randomised, double-blind
- Patients (n=667) with ABSSSI (FDA criteria)
- Oral tedizolid 200 mg once daily x 6 days versus oral linezolid 600 mg twice daily x 10 days

- Promising short course of treatment
- Significantly less thrombocytopenia (2.3% vs. 4.9%)
- On-going trial for pneumonia, but still not licensed
- Combination therapy with Gram-negative agent sometimes necessary

Prokocimer P, et al. *JAMA* 2013;309:559–569.

Dalbavancin vs. Linezolid/Vancomycin in the treatment of abSSSI

End Point	Dalbavancin	Vancomycin–Linezolid	Absolute Difference (95% CI)
	number/total number (percent)		*percentage points*
Primary end point			
DISCOVER 1	240/288 (83.3)	233/285 (81.8)	1.5 (–4.6 to 7.9)
DISCOVER 2	285/371 (76.8)	288/368 (78.3)	–1.5 (–7.4 to 4.6)
Both trials	525/659 (79.7)	521/653 (79.8)	–0.1 (–4.5 to 4.2)
Sensitivity analysis			
DISCOVER 1	259/288 (89.9)	259/285 (90.9)	–1.0 (–5.7 to 4.0)
DISCOVER 2	325/371 (87.6)	316/368 (85.9)	1.7 (–3.2 to 6.7)
Both trials	584/659 (88.6)	575/653 (88.1)	0.6 (–2.9 to 4.1)
Secondary end point			
Clinical status	517/570 (90.7)	502/545 (92.1)	–1.5 (–4.8 to 1.9)
Sensitivity analysis of clinical status†	533/570 (93.5)	517/545 (94.9)	–1.4 (–4.2 to 1.4)
Investigator's assessment of outcome	547/570 (96.0)	527/545 (96.7)	–0.7 (–3.0 to 1.5)

Boucher HW et al. N Eng J Med 2014

The new era of evidence-based medicine[1,2]

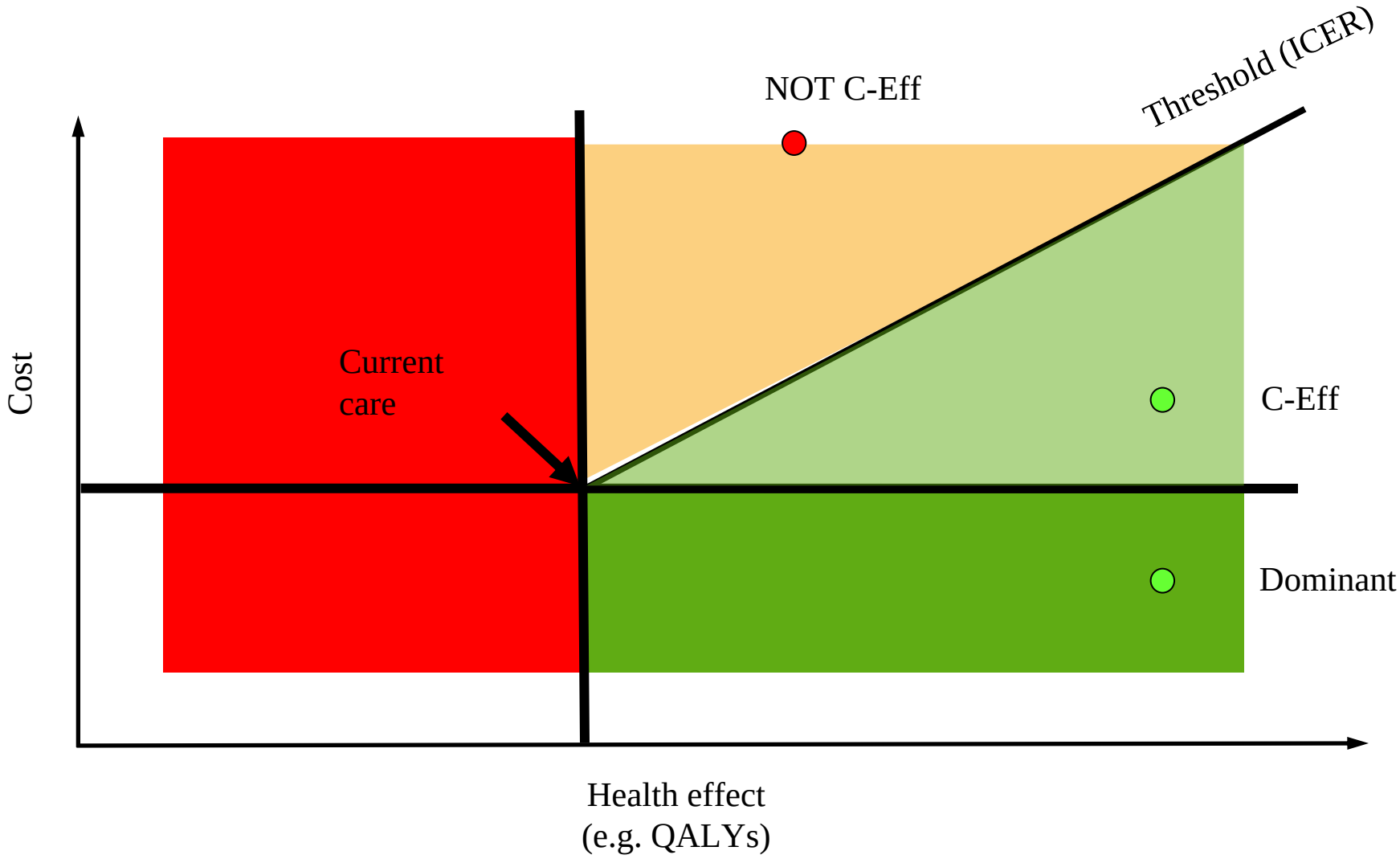
- Traditional requirements (for regulatory approval)
  - Efficacy
  - Safety

- Emerging requirements (for access/reimbursement and, to some degree, clinical use)
  - Clinical effectiveness (doing the right thing)
  - Efficiency (doing the thing right)
  - Costs
  - Patient outcomes (QoL)

QoL, quality of life.

1. Luce BR, et al. *Milbank Quart*. 2010;88:256–76; 2. Ward WJ, et al. *Healthc Financ Manage*. 2006;60:92–98.

The cost-effectiveness plane



C-Eff, cost-effective ; QALY, quality adjusted life year.

Annemans L. *Health economics for non-economists*. Academia Press, 2008.

Standard of care vs. new drugs to reduce economic burden in MRSA infections Possible reimbursement

- Included in DRG, effect seen on a larger scale (shorter LOS, less re-admissions)

- Extra payment for special drug with added value (applicable for Germany (“ZE”))

- Academic implementation I (Stewardship program)
- Academic implementation II (Cost-eff studies)

Adressing the sustainable use of antibiotics through an economic lens

Recommendation	Audience
The choice of antibiotic prescribing strategy should be made on the grounds of health economic analyses that take a longer-term perspective and more explicitly take into account costs, risks, and effects associated with resistance as well as the impact of different prescribing strategies on innovation within the market	Health economists supporting guideline committees, Health Technology Assessment and reimbursement agencies, etc.
Acknowledge resistance as a safety issue within regulation, using a longer time horizon to capture resistance-related safety risks leading to more restrictive labelling	Market authorization agency (e.g. EMA, FDA)
Reward pharmaceutical innovation independently of unit sales	Governments and international bodies via innovation funds

Morel CM et al. Clin Microbiol Infect 2017;23:718

Clinicians and health care economics our real relationsship in fighting infections

ID /
ICU/
Surgery

health
care
economics