Carbapenem resistant Enterobacteriaceae – how do we cope with them clinically?

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Imperial College Healthcare NHS
NHS Trust

What's the problem?

"CPE are nightmare bacteria."
Dr Tom Frieden, CDC Director

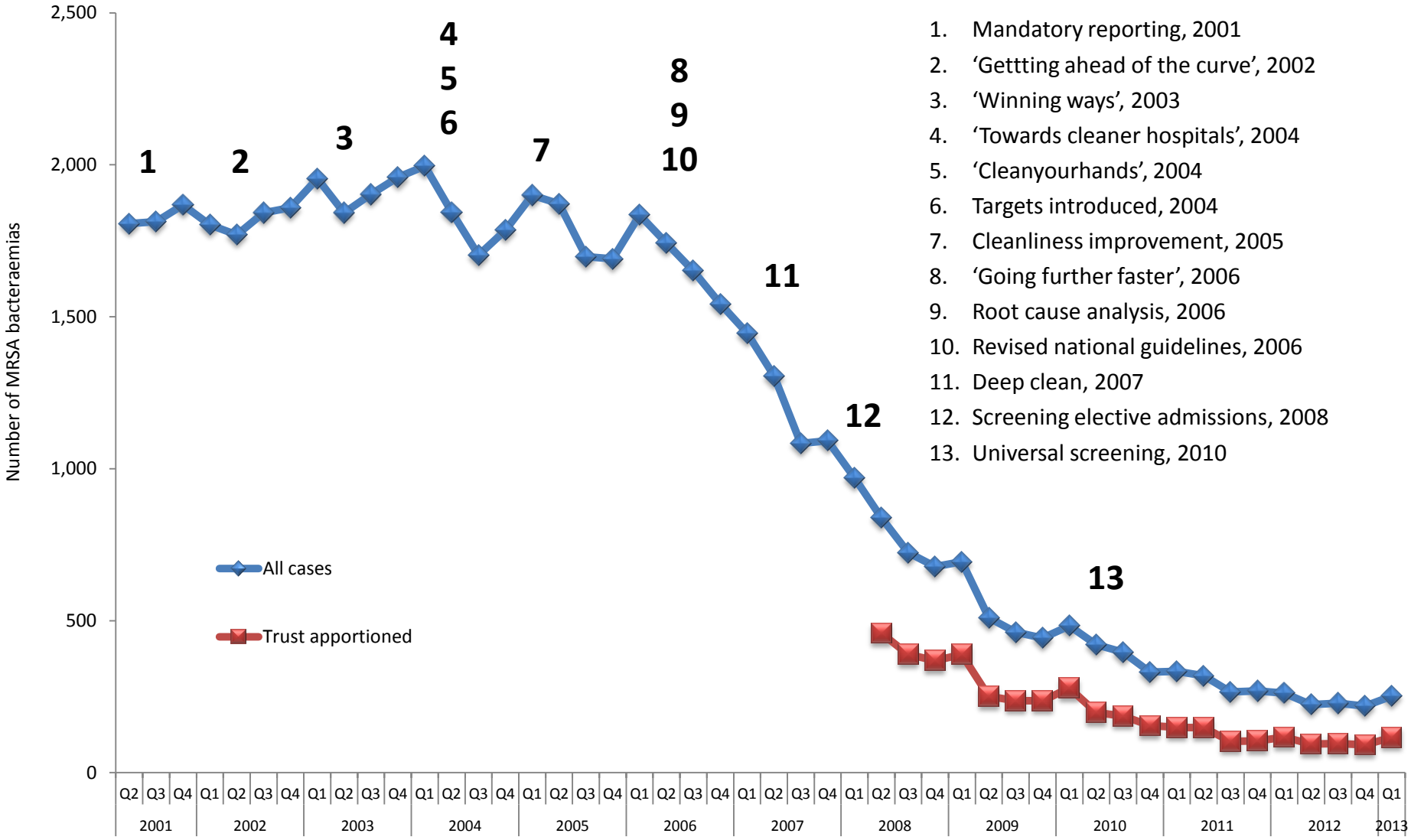
"If we don't take action, then we may all be back in an almost 19th Century environment where infections kill us as a result of routine operations."
Dame Sally Davies, Chief Medical Officer

"If we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work and we are cast back into the dark ages of medicine where treatable infections and injuries will kill once again."
David Cameron, Prime Minister, UK

"The rise of antibiotic-resistant bacteria, however, represents a serious threat to public health and the economy."
Barack Obama, President USA

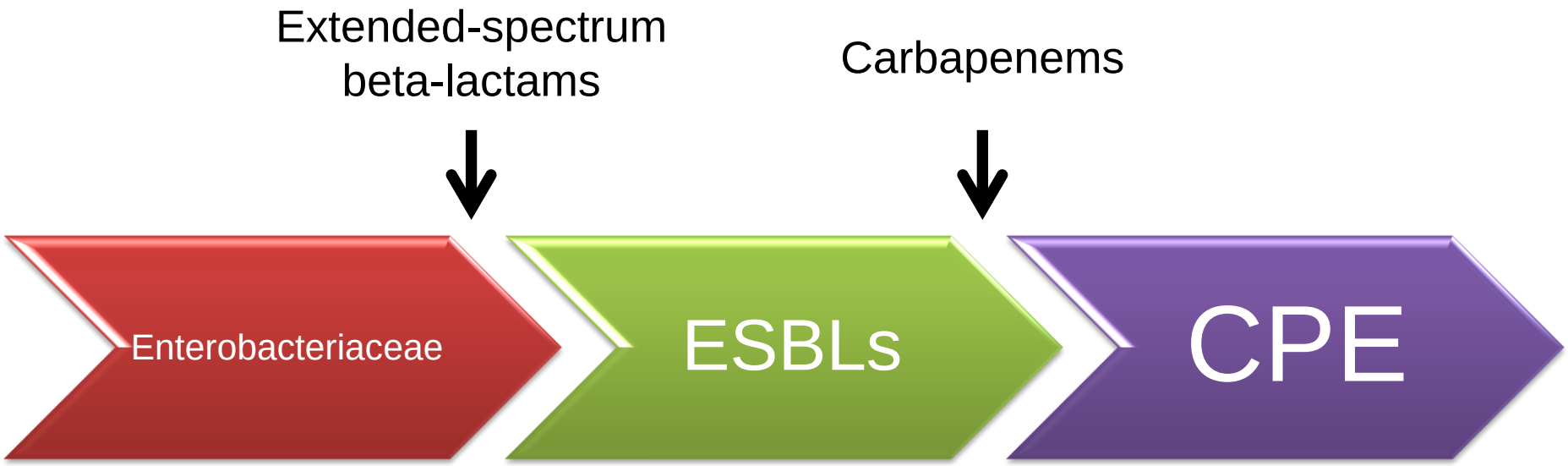
THE END OF ANTIBIOTICS IS NIGH

MRSA bacteraemia, England 2001-2013

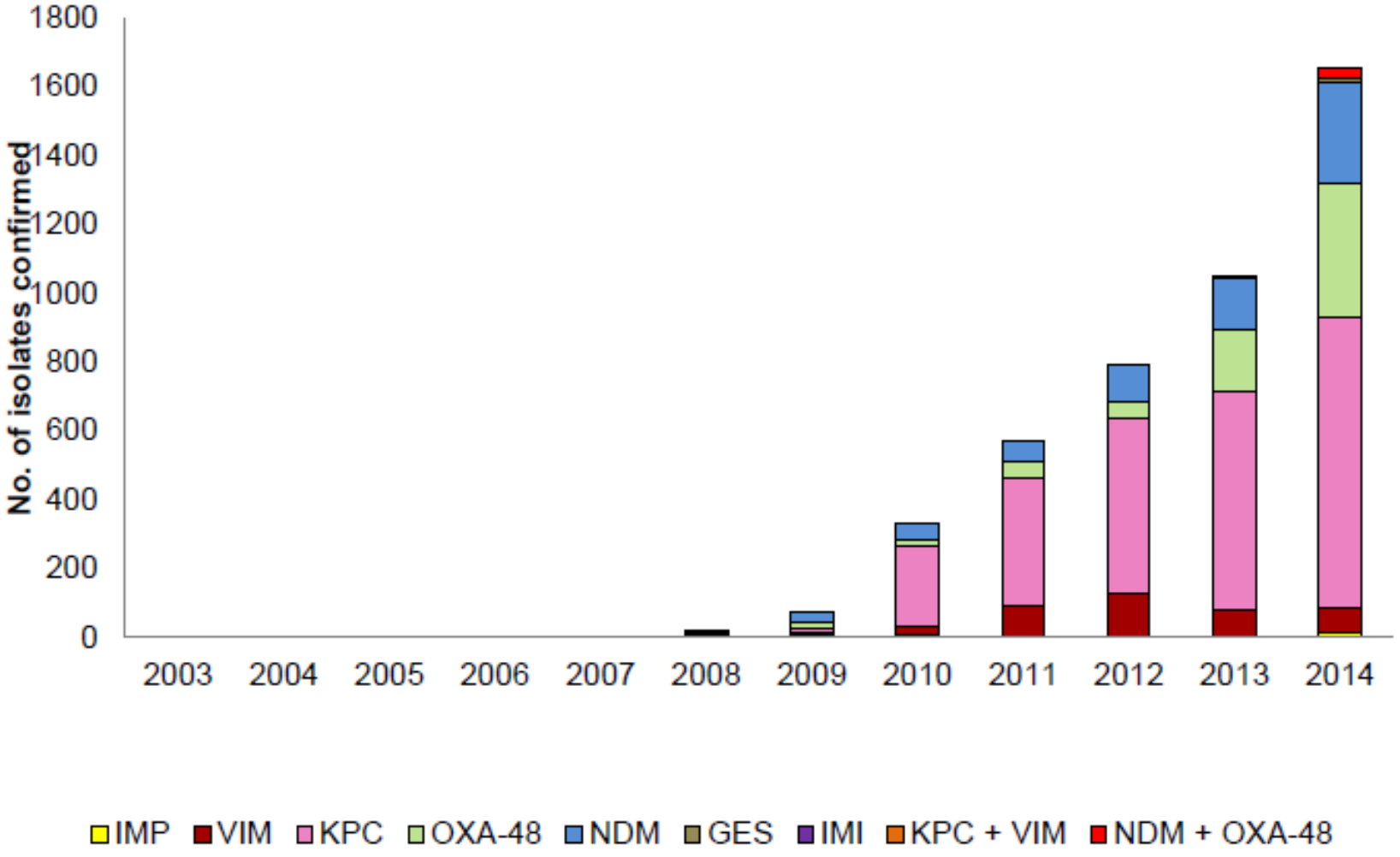


1. Mandatory reporting, 2001
2. 'Gettting ahead of the curve', 2002
3. 'Winning ways', 2003
4. 'Towards cleaner hospitals', 2004
5. 'Cleanyourhands', 2004
6. Targets introduced, 2004
7. Cleanliness improvement, 2005
8. 'Going further faster', 2006
9. Root cause analysis, 2006
10. Revised national guidelines, 2006
11. Deep clean, 2007
12. Screening elective admissions, 2008
13. Universal screening, 2010

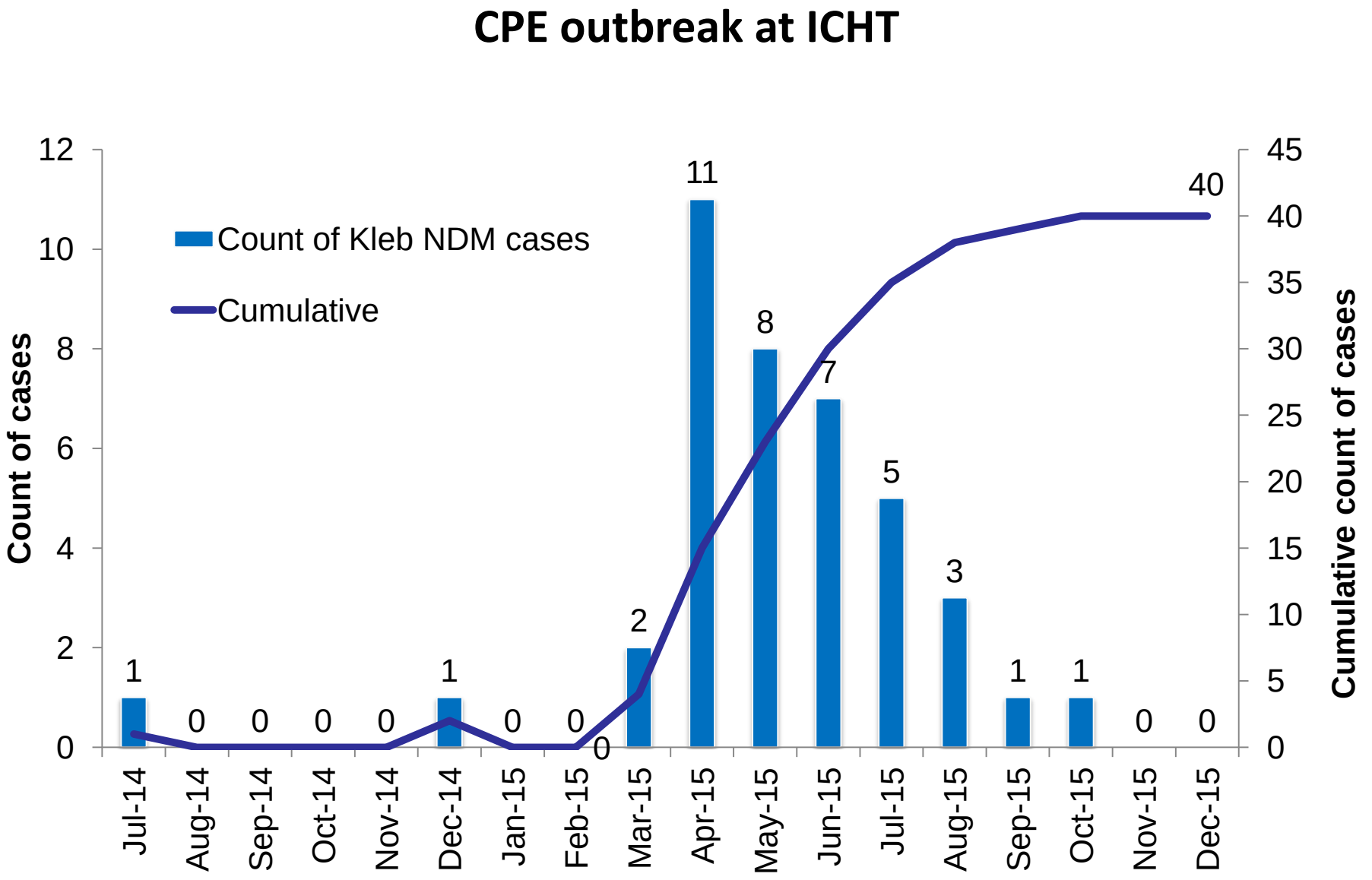
Creating a monster



CPE reported to PHE's reference lab



ESPAUR 2015.


CPE outbreak at ICHT
Count of Kleb NDM cases
Cumulative
Count of cases
Cumulative count of cases
0
2
4
6
8
10
12
0
5
10
15
20
25
30
35
40
45
1
0
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0
0
1
0
0
2
11
8
7
5
3
1
1
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0
Jul-14
Aug-14
Sep-14
Oct-14
Nov-14
Dec-14
Jan-15
Feb-15
Mar-15
Apr-15
May-15
Jun-15
Jul-15
Aug-15
Sep-15
Oct-15
Nov-15
Dec-15

CPE screening: key clinical questions

- What is the rate of carriage on admission?
- How good are we at the admission screening programme?
- What value to serial admission screens to confirm a negative carriage status?
- Is there a major reservoir of CPE in outpatient haemodialysis units?

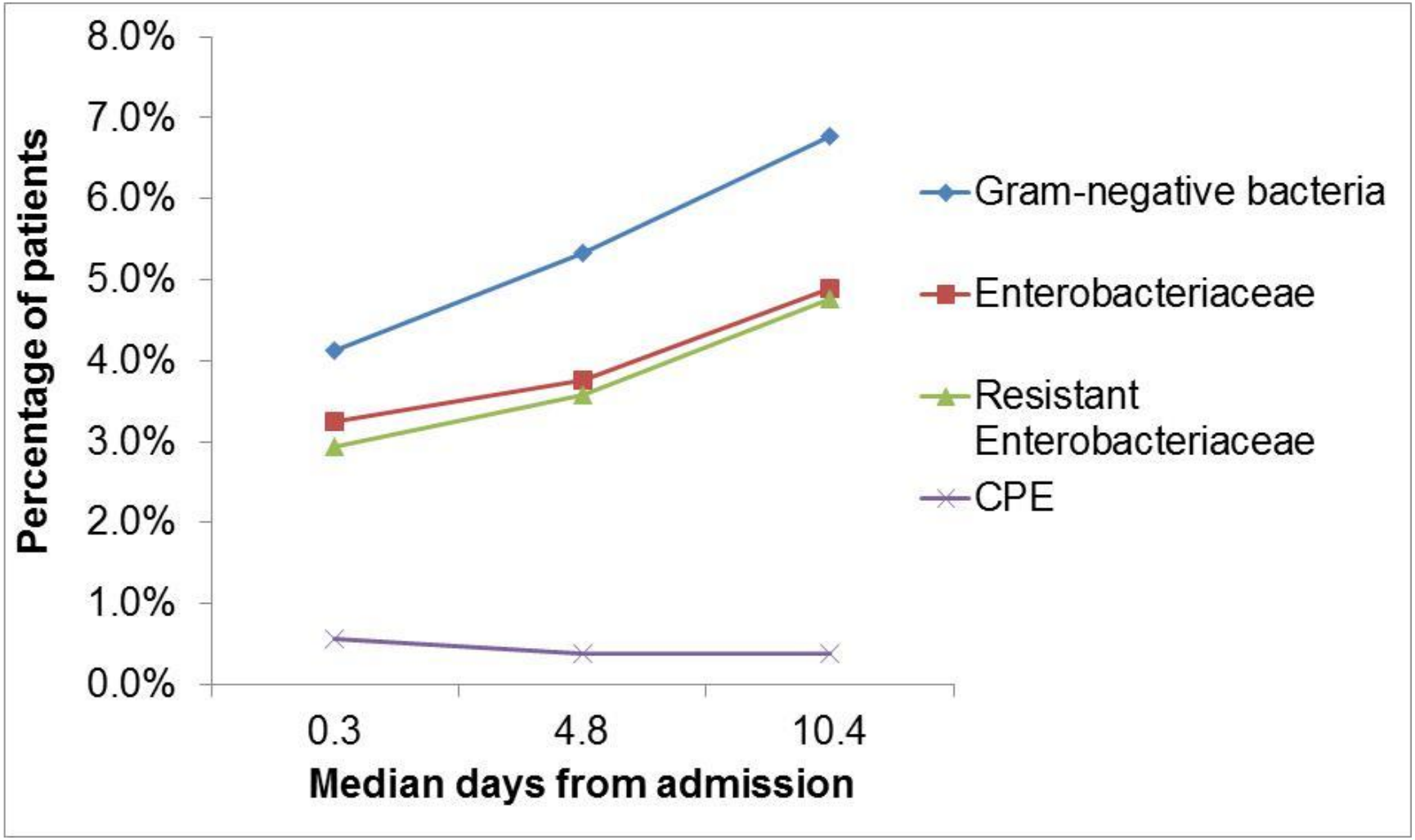
- **Large dataset comprising 15,551 CPE rectal screens from a total of 7,673 patients between June and December 2015, linked with hospital admissions database.**

Results: value of serial screens

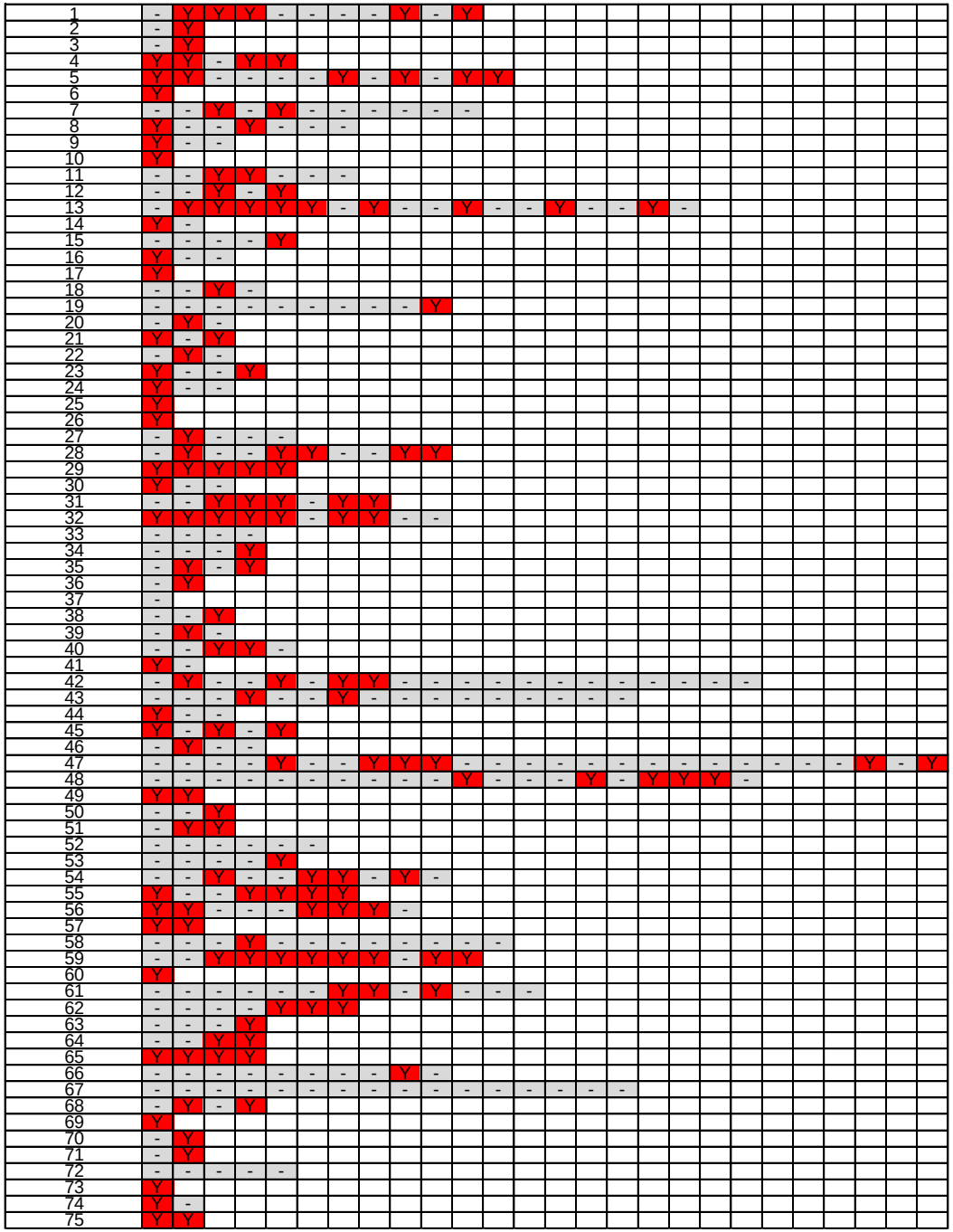
	Screen 1 (within 24 hour)		Screen 2 (25-72 hours)		Screen 3 (73-120 hours)	
	n	%	n	%	n	%
Number of patients	3932	-	1652	-	1227	-
Gram-negative bacteria	161	4.1	38	2.3	45	3.7
Enterobacteriaceae	108	2.7	29	1.8	41	3.3
Resistant Enterobacteriaceae	80	2.0	21	1.3	24	2.0
CPE	22	0.5	2	0.1	3	0.2

- **Serial admission screens add no value in confirming a negative carriage status**

But…repeated screening makes sense!



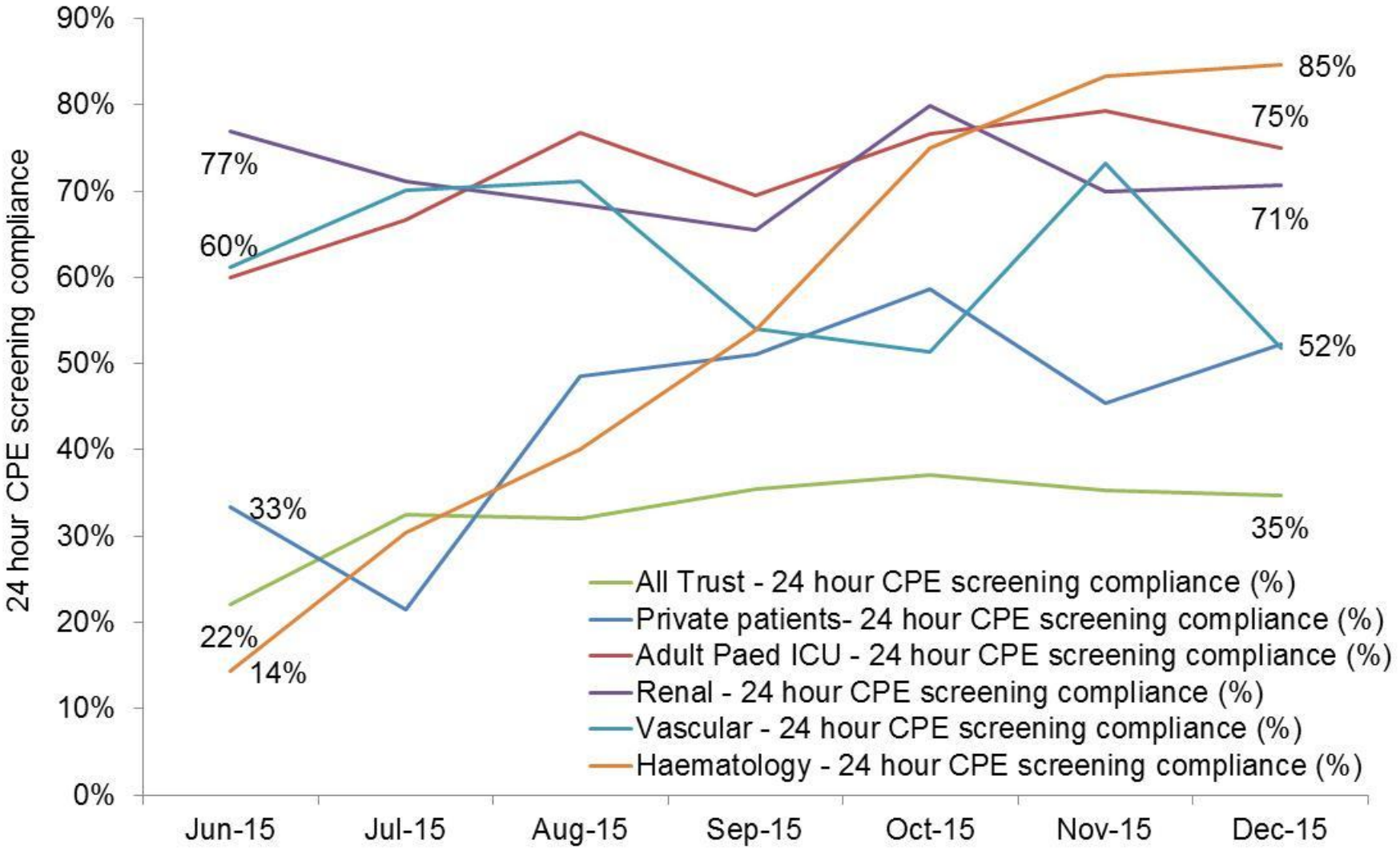
Data from 1597 patients who received 3 CPE screens during hospitalisation between June and December 2015.



Once positive, always positi

Serial CPE rectal screens from 75 patients who were found to be CPE positive during June – September 2015..

CPE admission screening compliance



Data from 3067 admissions between June and December 2015.

Rising threat from MDR-GNR

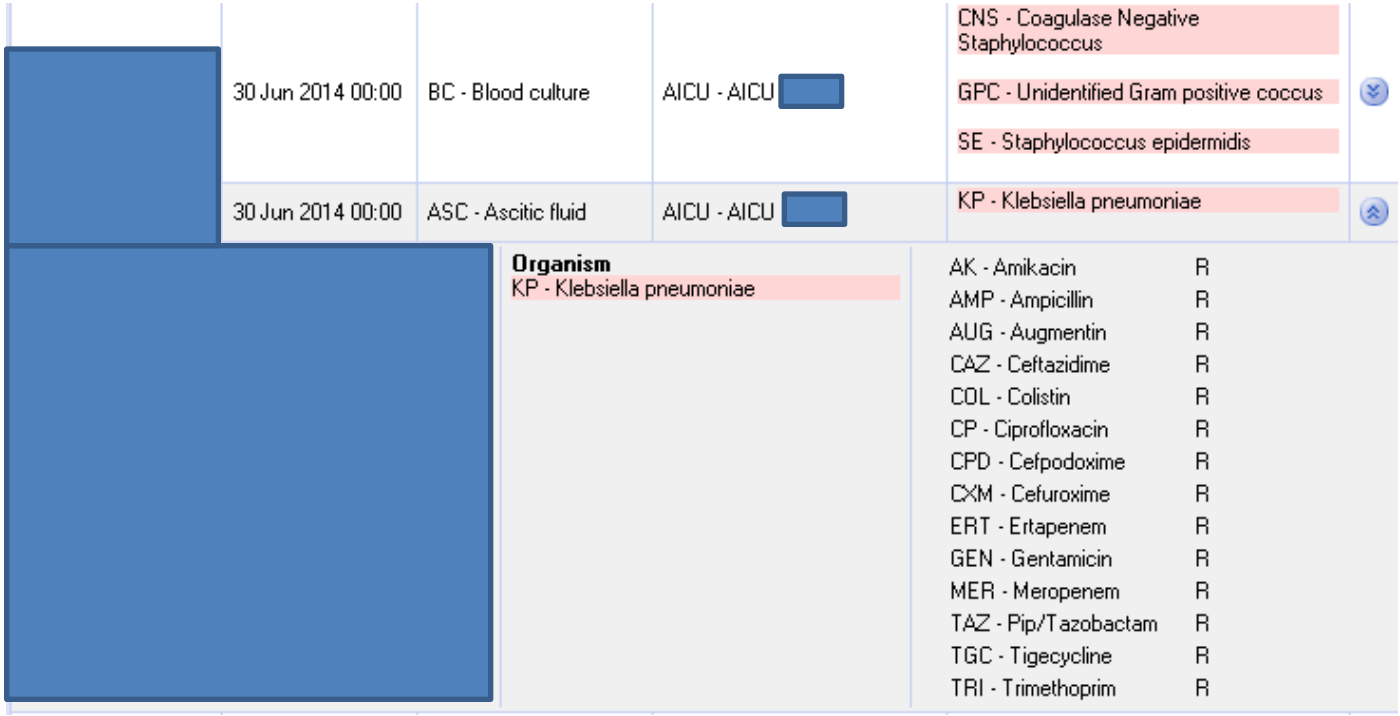
% of all HAI caused by GNRs.

% of ICU HAI caused by GNRs.

Non-fermenters	***Acinetobacter baumannii*** ***Pseudomonas aeruginosa*** ***Stenotrophomonas maltophilia***	**CPO**
Enterobacteriaceae	*Klebsiella pneumoniae* *Escherichia coli* *Enterobacter cloacae*	**CPE**

Hidron et al. *Infect Control Hosp Epidemiol* 2008;29:966-1011.
Peleg & Hooper. *N Engl J Med* 2010;362:1804-1813.

What's the problem? Resistance



Courtesy of Pat Cattini

What's the problem? Mortality

	Enterobacteriaceae		Non fermenters
Organism	AmpC / ESBL	CPE	*A. baumannii*
Attributable mortality	Moderate	Massive (>50%)	Minimal

Shorr *et al. Crit Care Med* 2009;37:1463-1469.
Patel *et al. Iinfect Control Hosp Epidemiol* 2008;29:1099-1106.

Colistin dosing

MAJOR ARTICLE

High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

Lidia Dalfino,[1] Filomena Puntillo,[1] Adriana Mosca,[2] Rosa Monno,[2] Maria Luigia Spada,[1] Sara Coppolecchia,[1] Giuseppe Miragliotta,[2] Francesco Bruno,[1] and Nicola Brienza[1]

[1]Anesthesia and Intensive Care Unit, Department of Emergency and Organ Transplantion; and [2]Microbiology Section, Department of Interdisciplinary Medicine, University of Bari, Italy

(See the Editorial Commentary by Roberts and Lipman, on pages 1727–9.)

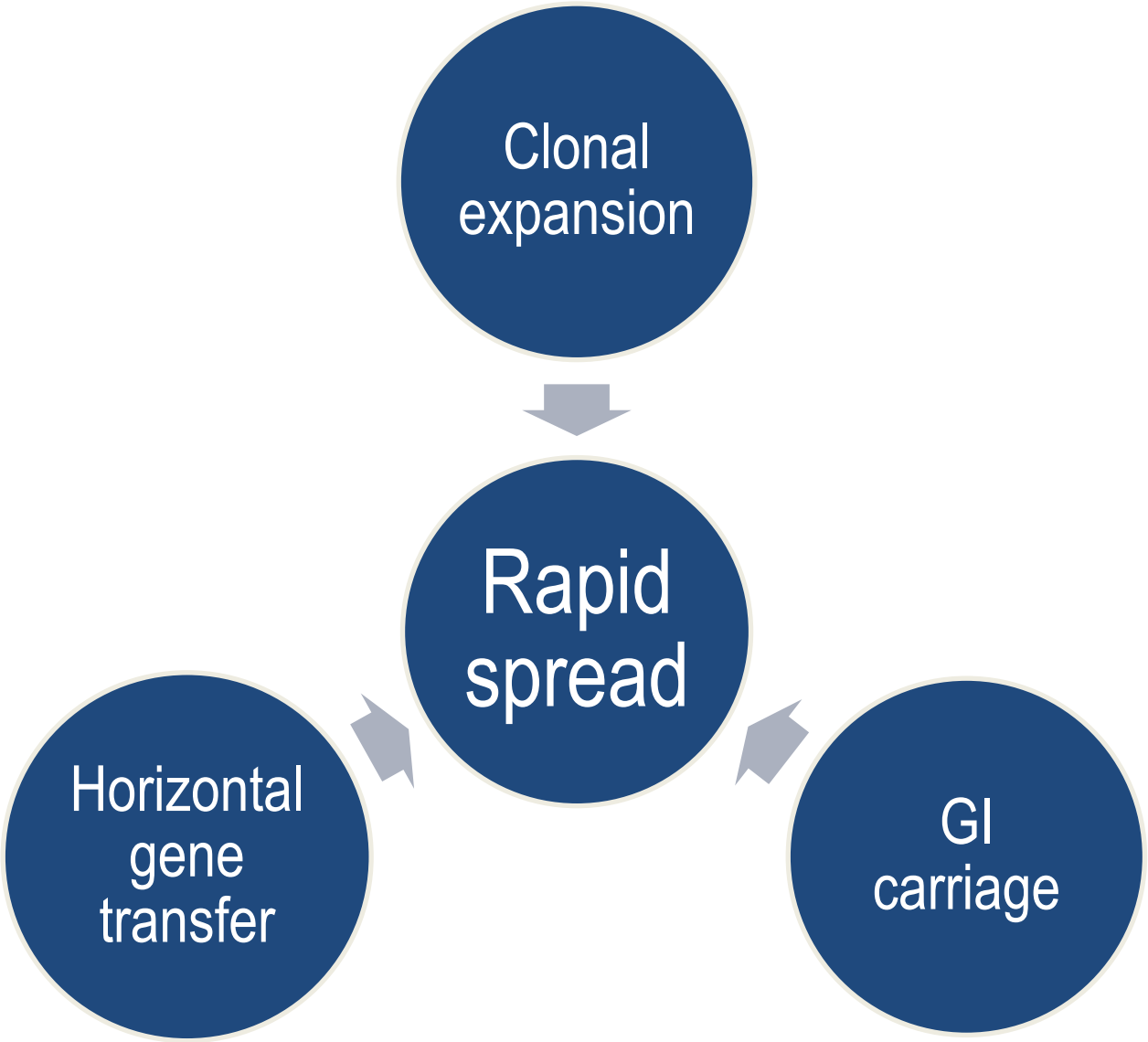
Background. Gram-negative bacteria susceptible only to colistin (COS) are emerging causes of severe nosocomial infections, reviving interest in the use of colistin. However, consensus on the most effective way to administer colistin has not yet been reached.

Methods. All patients who had sepsis due to COS gram-negative bacteria or minimally susceptible gram-negative bacteria and received intravenous colistimethate sodium (CMS) were prospectively enrolled. The CMS dosing schedule was based on a loading dose of 9 MU and a 9-MU twice-daily fractioned maintenance dose, titrated on renal function. For each CMS course, clinical cure, bacteriological clearance, daily serum creatinine clearance, and estimated creatinine clearance were recorded.

Results. Twenty-eight infectious episodes due to *Acinetobacter baumannii* (46.4%), *Klebsiella pneumoniae* (46.4%), and *Pseudomonas aeruginosa* (7.2%) were analyzed. The main types of infection were bloodstream infection (64.3%) and ventilator-associated pneumonia (35.7%). Clinical cure was observed in 23 cases (82.1%). Acute kidney injury developed during 5 treatment courses (17.8%), did not require renal replacement therapy, and subsided within 10 days from CMS discontinuation. No correlation was found between variation in serum creatinine level (from baseline to peak) and daily and cumulative doses of CMS, and between variation in serum creatinine level (from baseline to peak) and duration of CMS treatment.

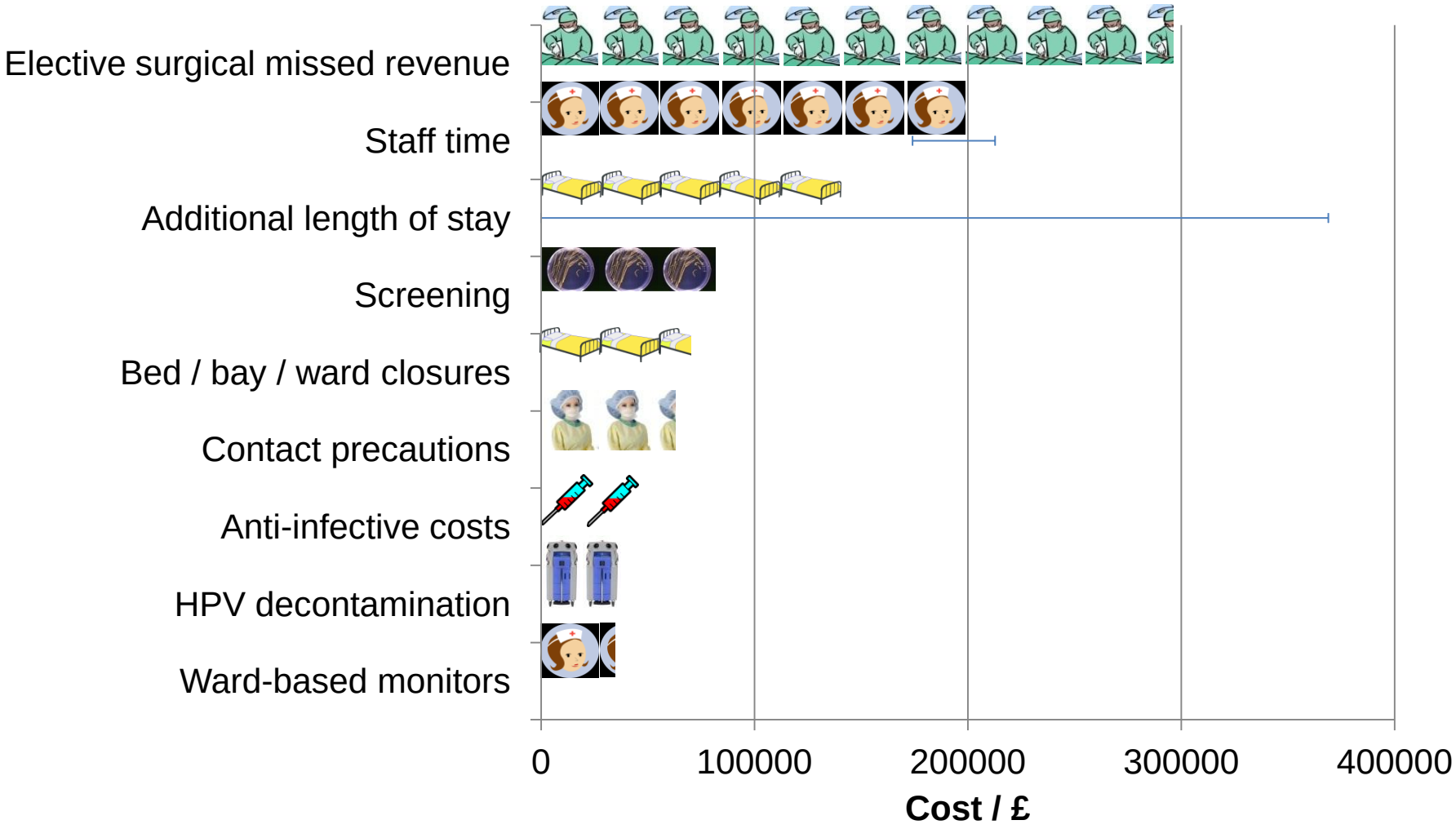
Conclusions. Our study shows that in severe infections due to COS gram-negative bacteria, the high-dose, extended-interval CMS regimen has a high efficacy, without significant renal toxicity.

What's the problem? Rapid spread



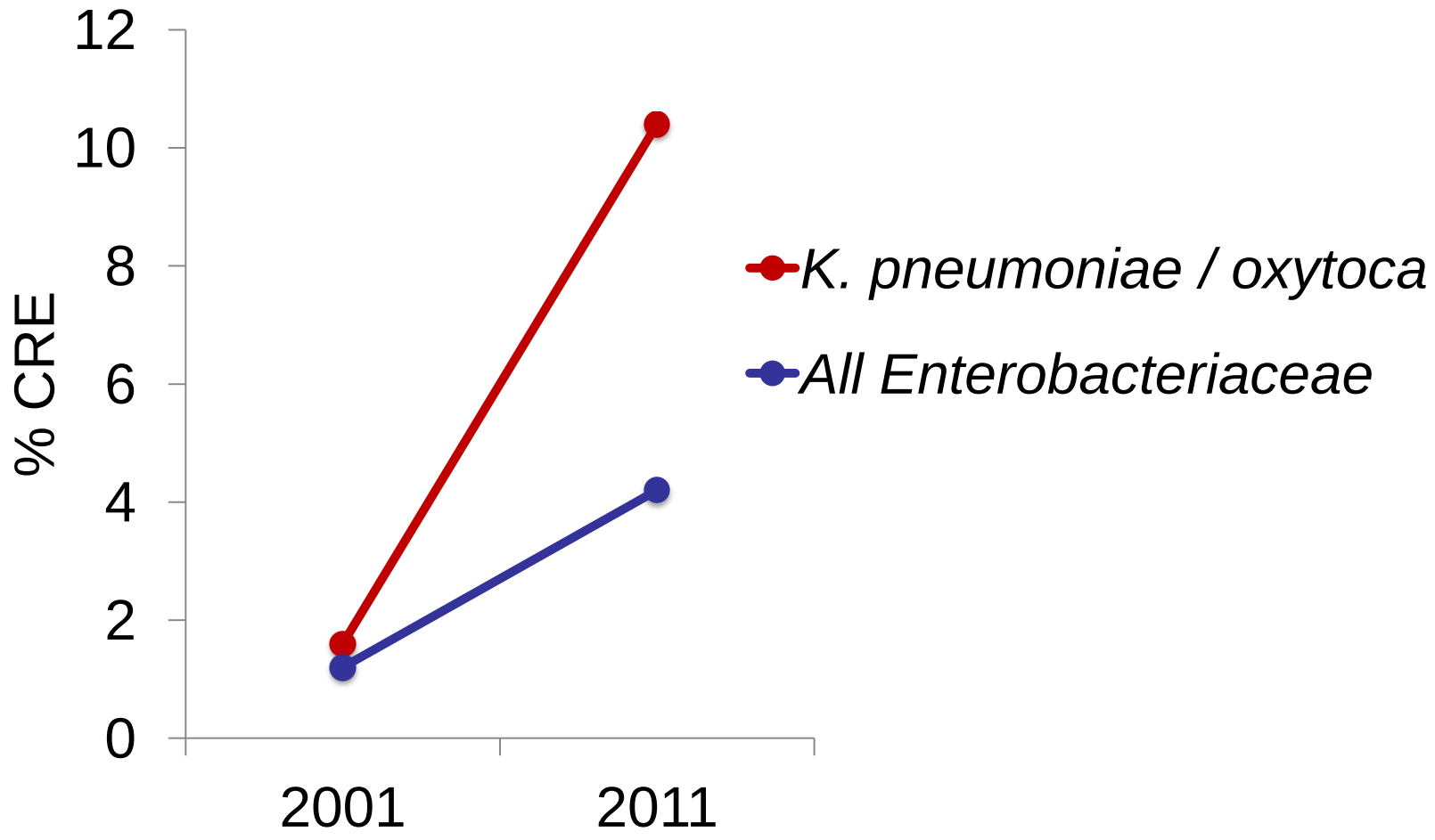
Counting the cost of CPE

Economic evaluation of a 40 case outbreak of CPE. Error bars represent range



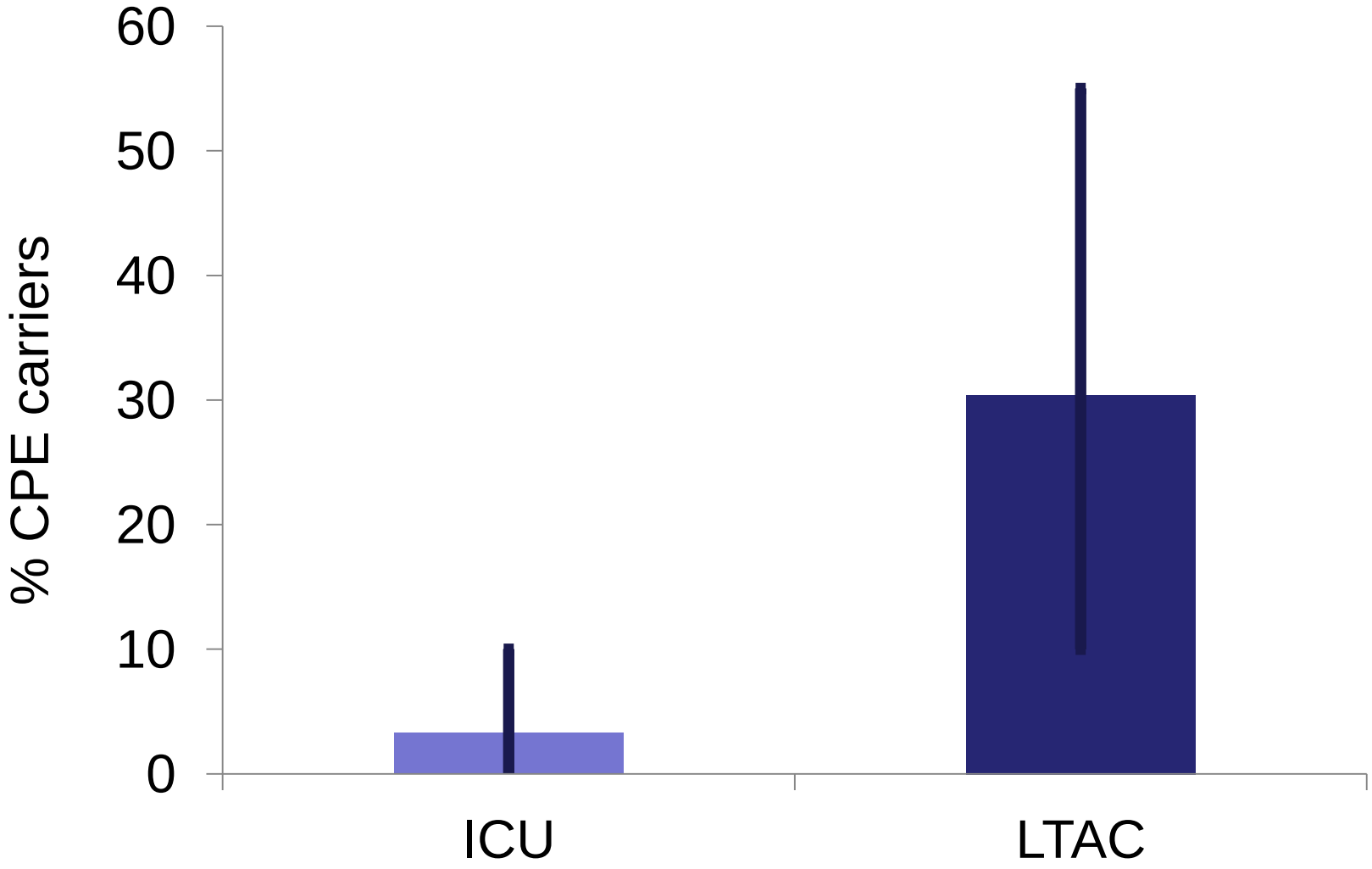
Otter *et al. Clin Microbiol Infect* 2016 in press.

CPE in the USA



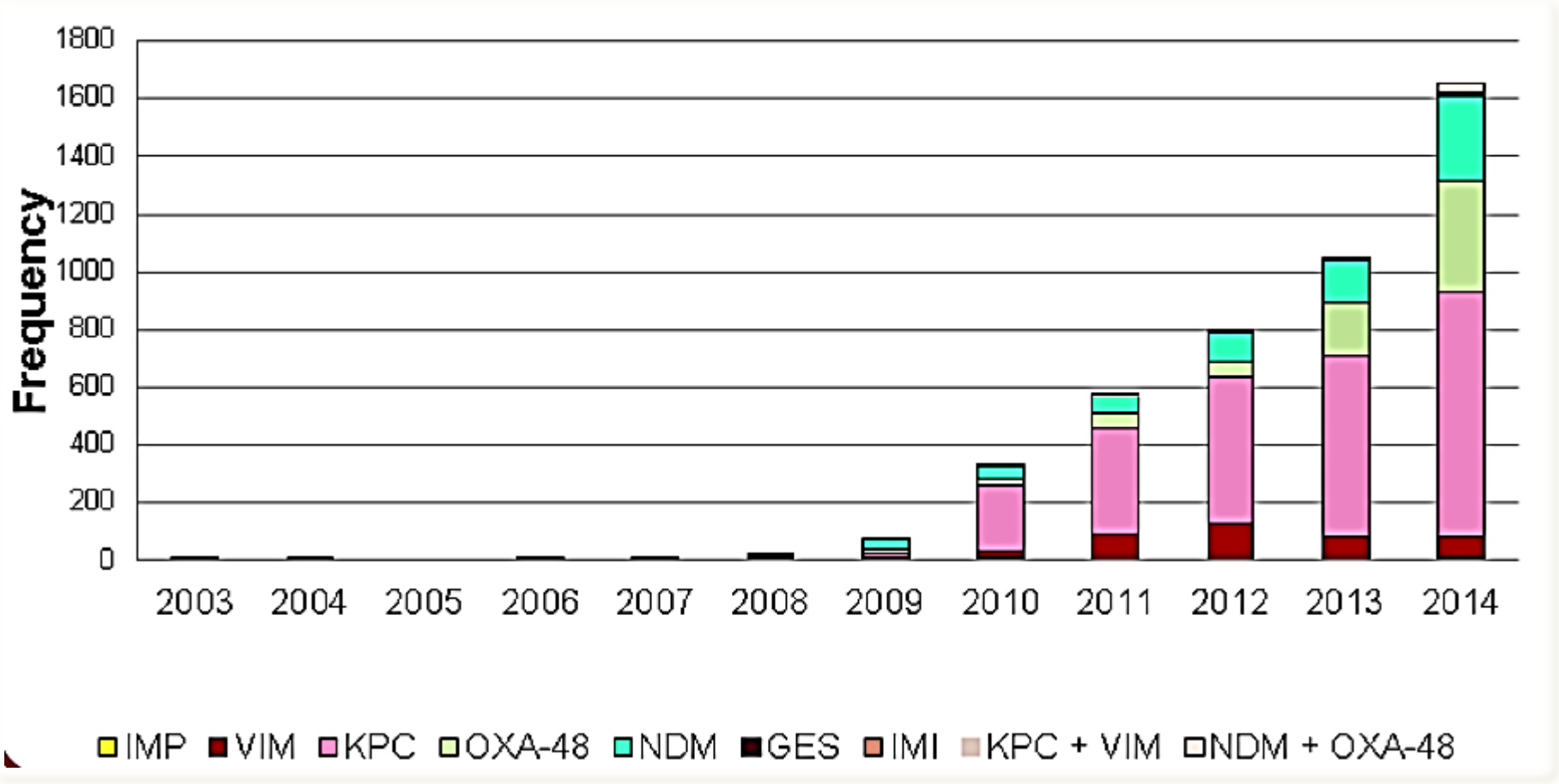
NHSN / NNIS data; *MMWR* 2013;62:165-170.

CPE in LTACs, USA



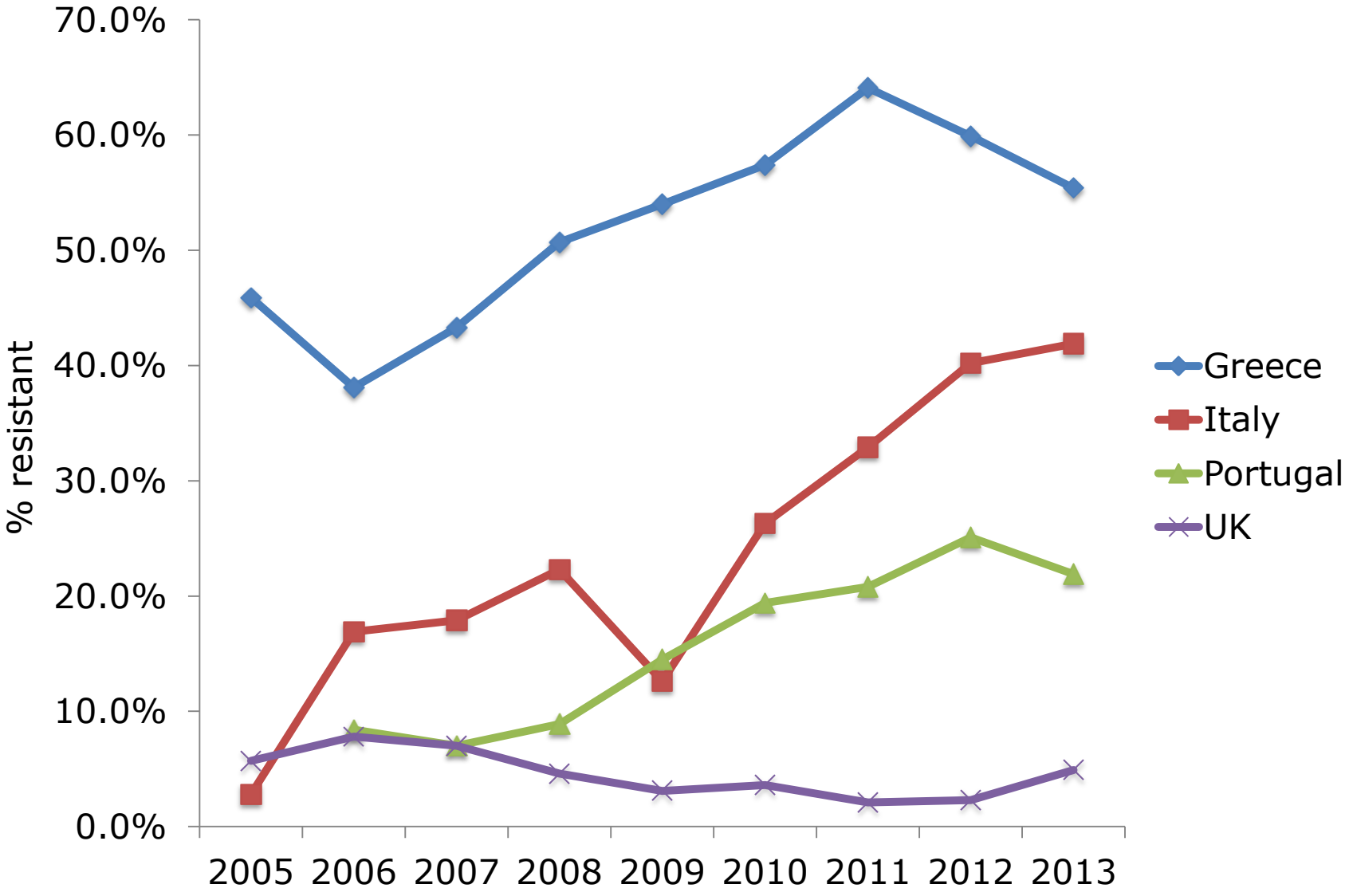
Lin *et al. Clin Infect Dis* 2013;57:1246-1252.

Emergence of CPE in the UK



PHE.

Invasive multidrug-resistant *K. pneumoniae*



EARS-Net

Colistin resistance in Italy

Survey of 191 CPE from 21 labs across Italy.

43%

Colistin resistant *K. pneumoniae*.
Range = 10-80% for the 21 labs.

Monaco *et al.* 2014; *Euro Surveill* 2014;19:pii=20939.

Simple, stark, sobering sums

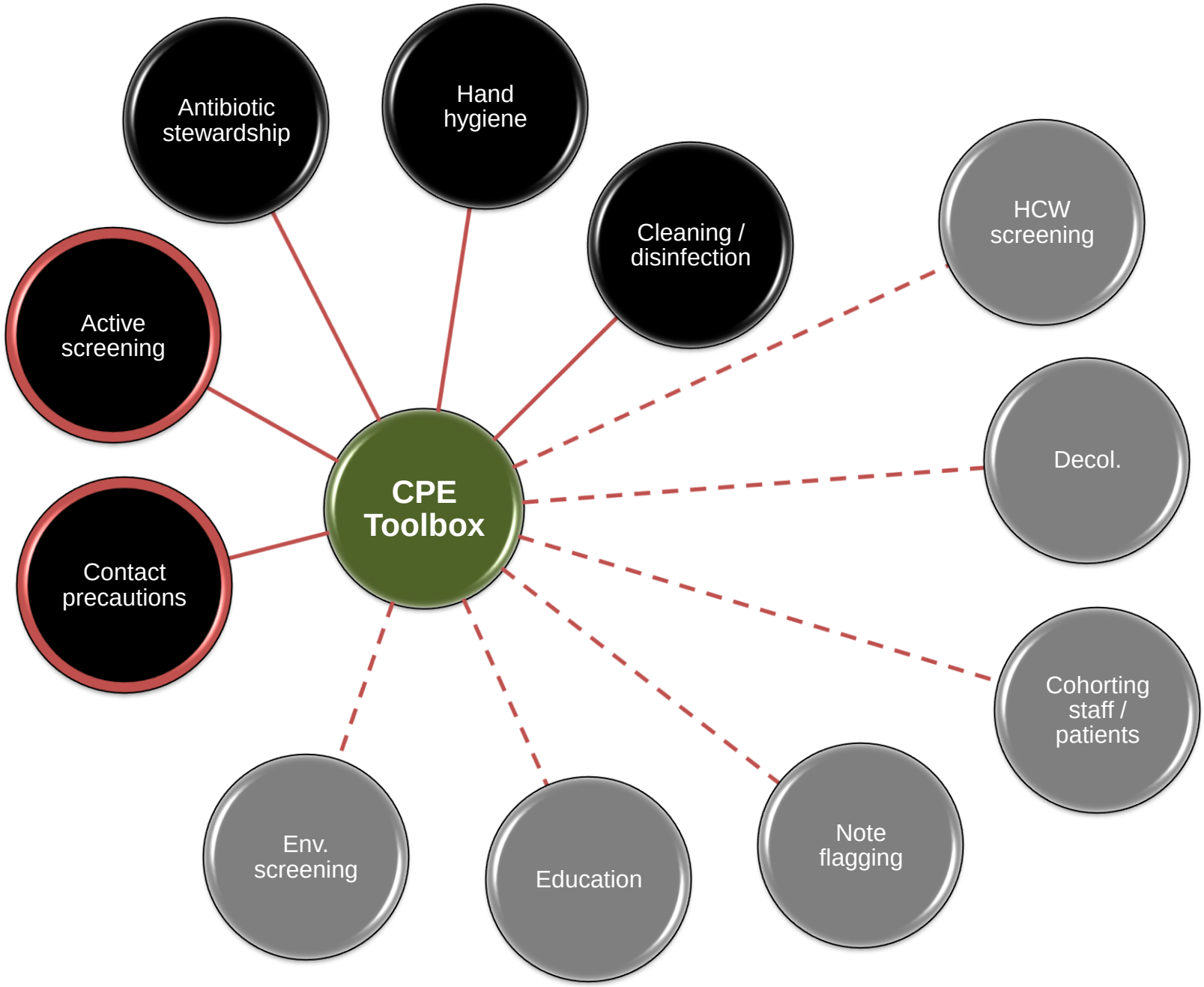
$0.5\%^{1} \times 186{,}393 = 932$ (!)

$0.1\%^{2} \times 186{,}393 = 186$

$0.1\% \times 15.892\text{m}^{*} = 15{,}892$

* Admissions to NHS acute hospitals, Financial Year 14/15. NHS Confederation, Key Statistics on the NHS,

1. Mookerjee *et al.* ECCMID 2016.
2. Otter *et al. J Antimicrob Chemother* 2016 in press.



Otter *et al. Clin Microbiol Infect* 2015 2015;21:1057–1066.

Who do I screen?

UK PHE CPE Toolkit screening triggers:

a) an inpatient in a hospital abroad, or

b) an inpatient in a UK hospital which has problems with spread of CPE (if known), or

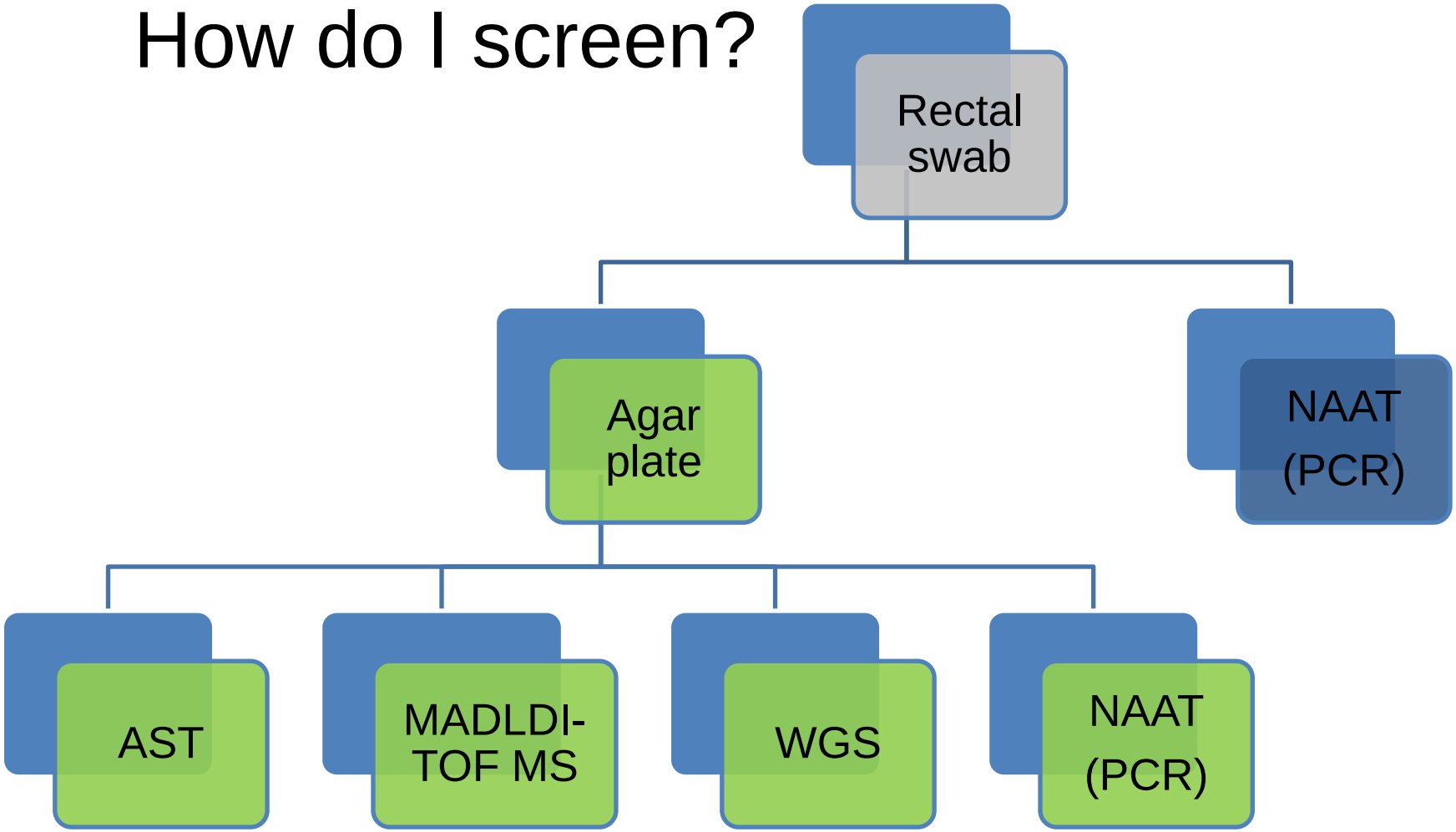
c) a 'previously' positive case.

Also consider screening admissions to high-risk units such as ICU, and patients who live overseas.

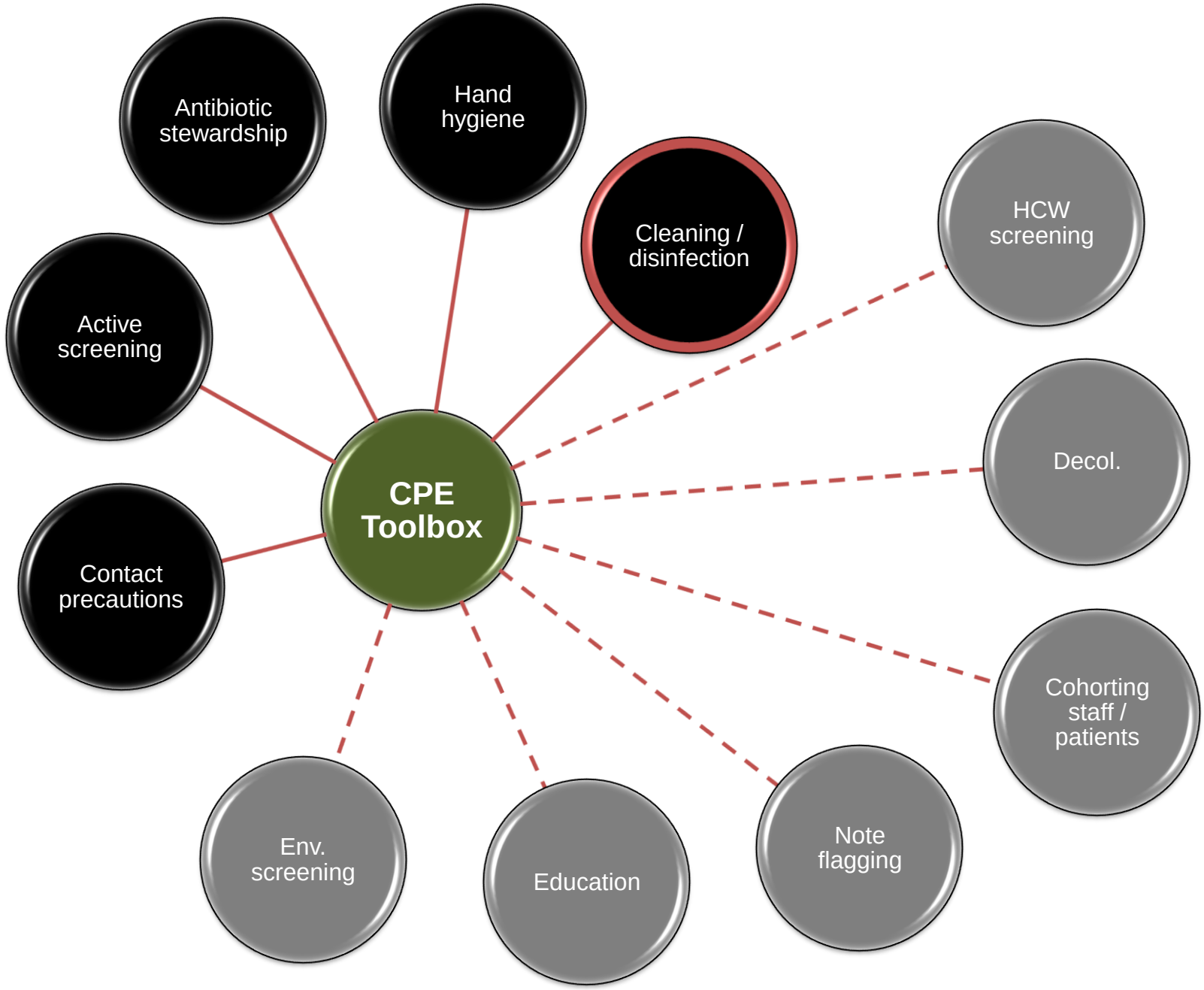
How do I screen?

- Rectal swab is the best sample
  - Insert no more than 2cm into rectum
  - Twist gently and withdraw
  - Ideally want to see faeces on swab.
- Patient and staff education as to why this is needed in order to overcome taboos
- Alternate specimen is stool sample, but have to wait for the patient to ‘go’

How do I screen?

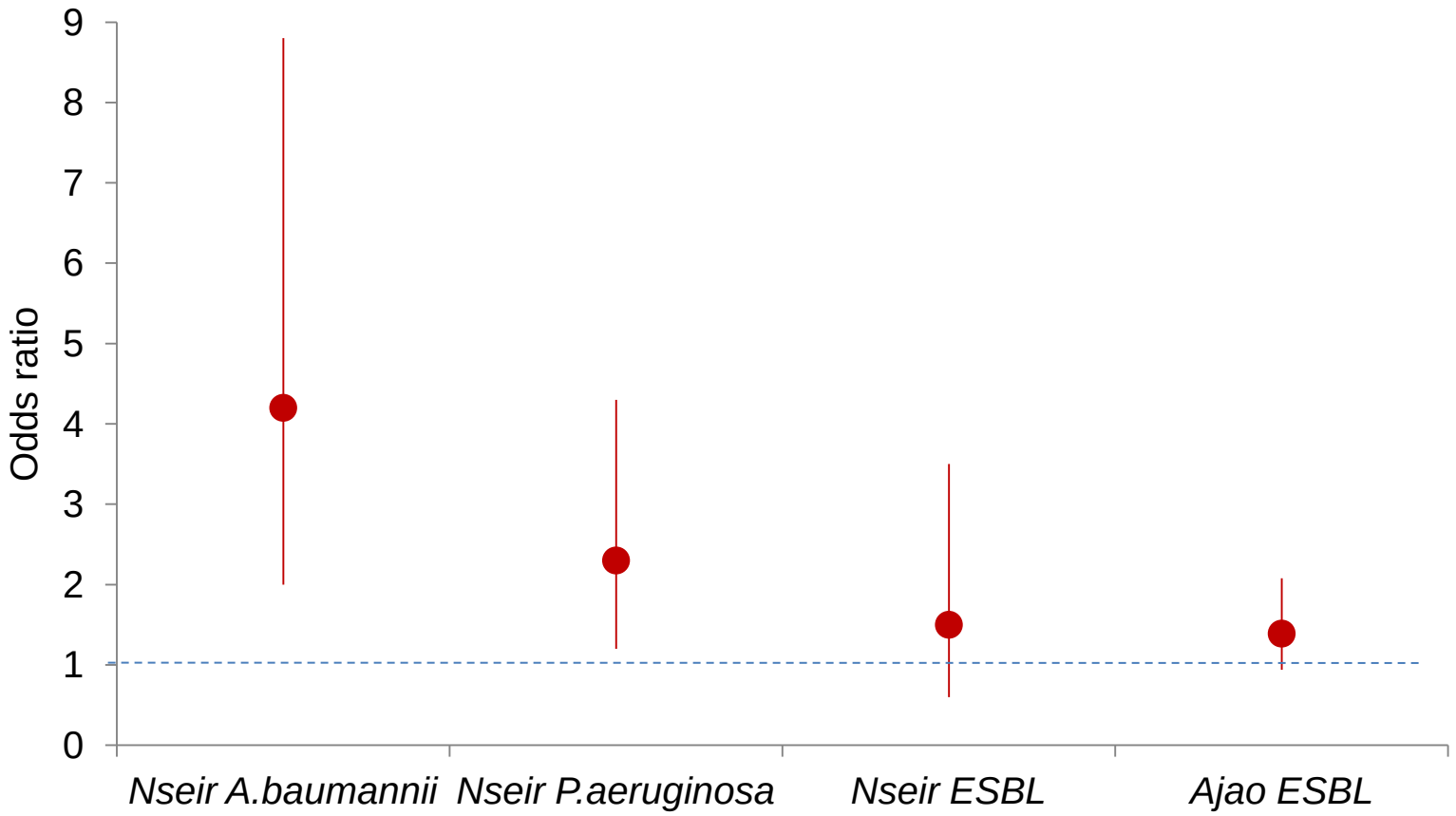


NAAT = nucleic acid amplification techniques
AST = antimicrobial susceptibility testing
MALDI-TOF = Matrix-assisted laser desorption /ionization – time of flight mass spectrometry
WGS = whole genome sequencing



Otter *et al. Clin Microbiol Infect* 2015 2015;21:1057–1066.

The bed location lottery

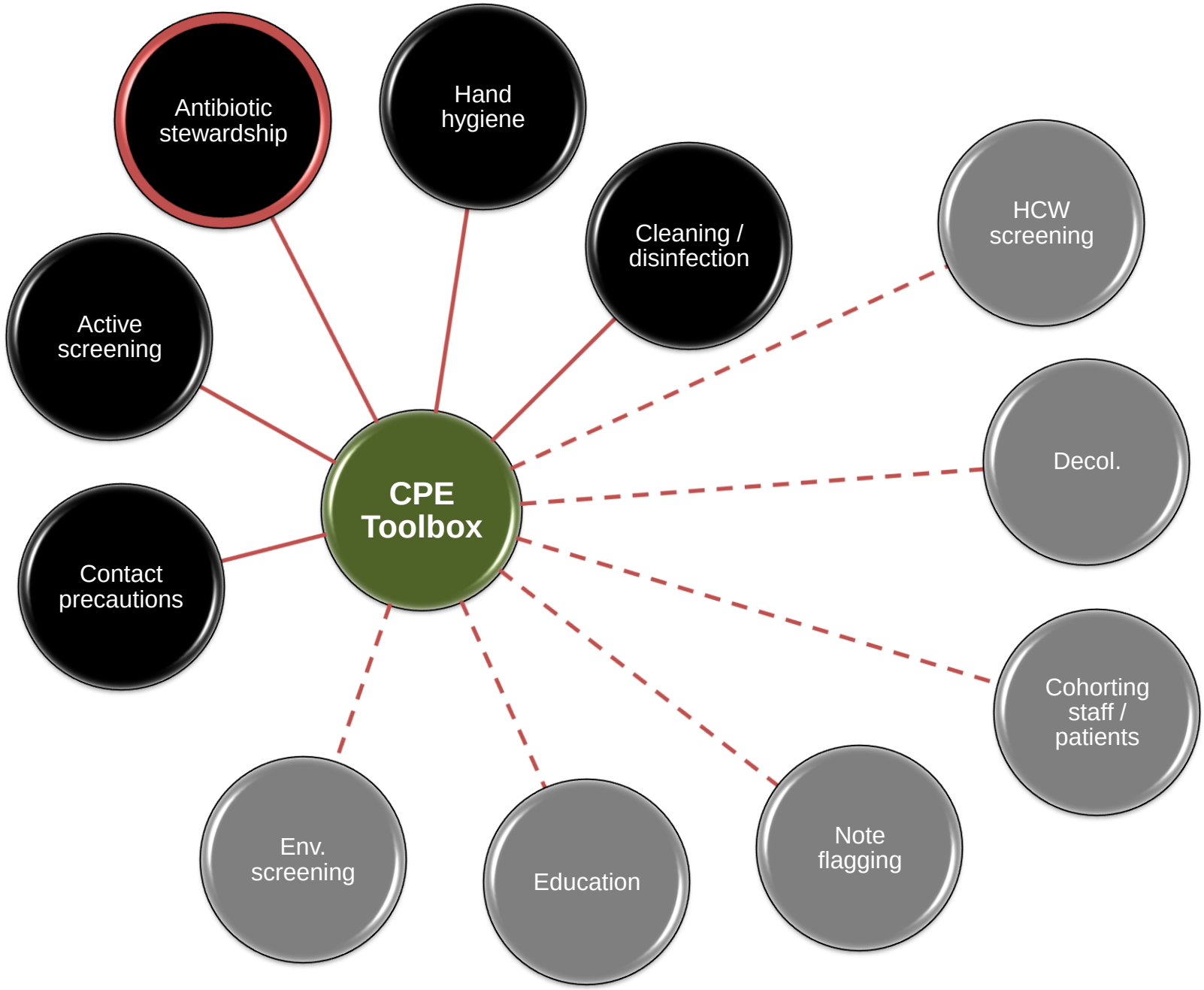


Nseir *et al. Clin Microbiol Infect* 2011;17:1201-1208.
Ajao *et al. Infect Control Hosp Epidemiol* 2013;34:453-458.

MDR-GNB cleaning & disinfection checklist

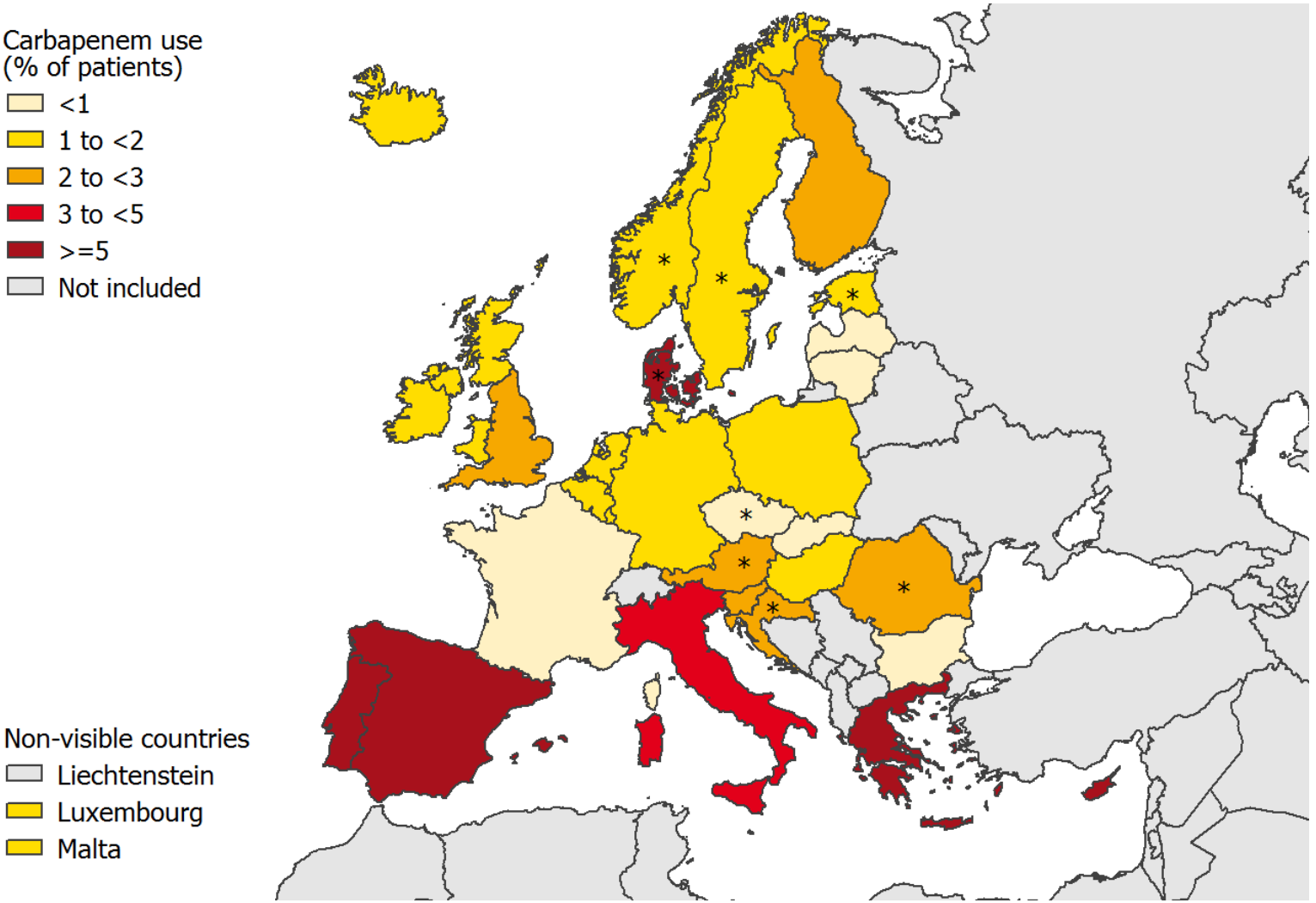
- ❑ Clean / declutter
- ❑ Monitor cleaning process (e.g. fluorescent markers)
- ❑ All equipment disinfected before leaving room
- ❑ Enhanced daily disinfection using bleach
- ❑ Terminal disinfection using bleach or, ideally, H_2O_2 vapor[1-3]

1. Gopinath *et al. Infect Control Hosp Epidemiol* 2013;34:99-100.
2. Snitkin *et al. Sci Transl Med* 2012;4:148ra116.
3. Verma *et al. J Infect Prevent* 2013;7:S37.



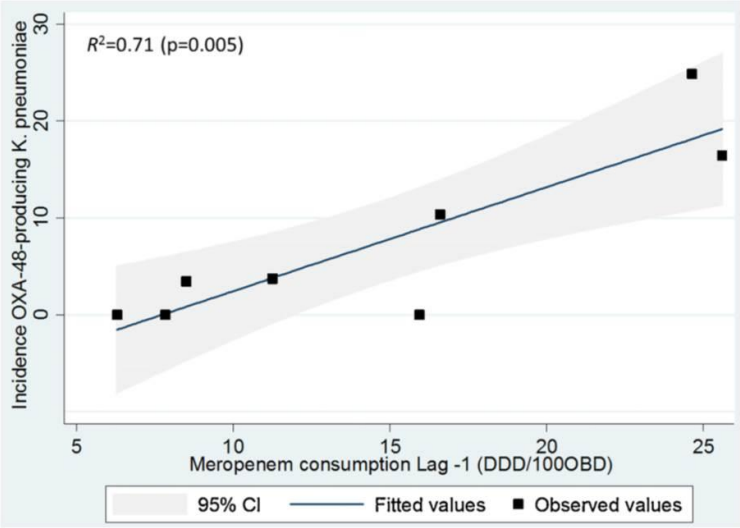
Otter *et al. Clin Microbiol Infect* 2015 2015;21:1057–1066.

Carbapenem use, Europe



ECDC point prevalence survey 2013.

Can we forecast a CPE storm?



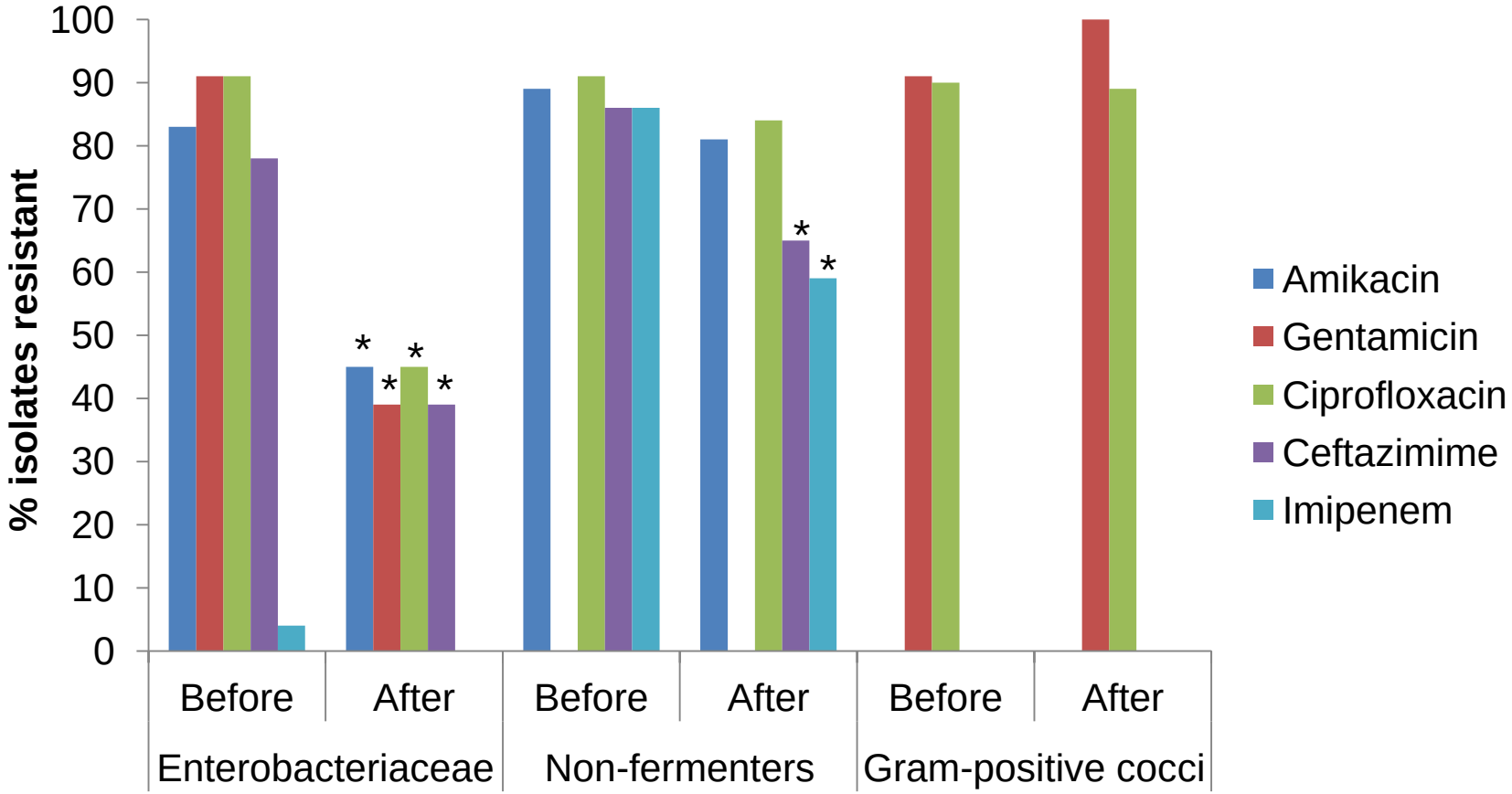
What drives carbapenem resistance? The use of meropenem in the previous year plotted against the incidence rate of OXA-48-producing K. pneumoniae

- Could we find and implement an “alert” level of carbapenem use?
- The authors claim a stewardship intervention brought the CPE outbreak under control – but also implemented ‘case isolation, screening of contacts, barrier nursing and other infection control interventions’.
- Study focussed only on OXA-48 *K. pneumoniae*; what about other Enterobacteriaceae and non-fermenters.

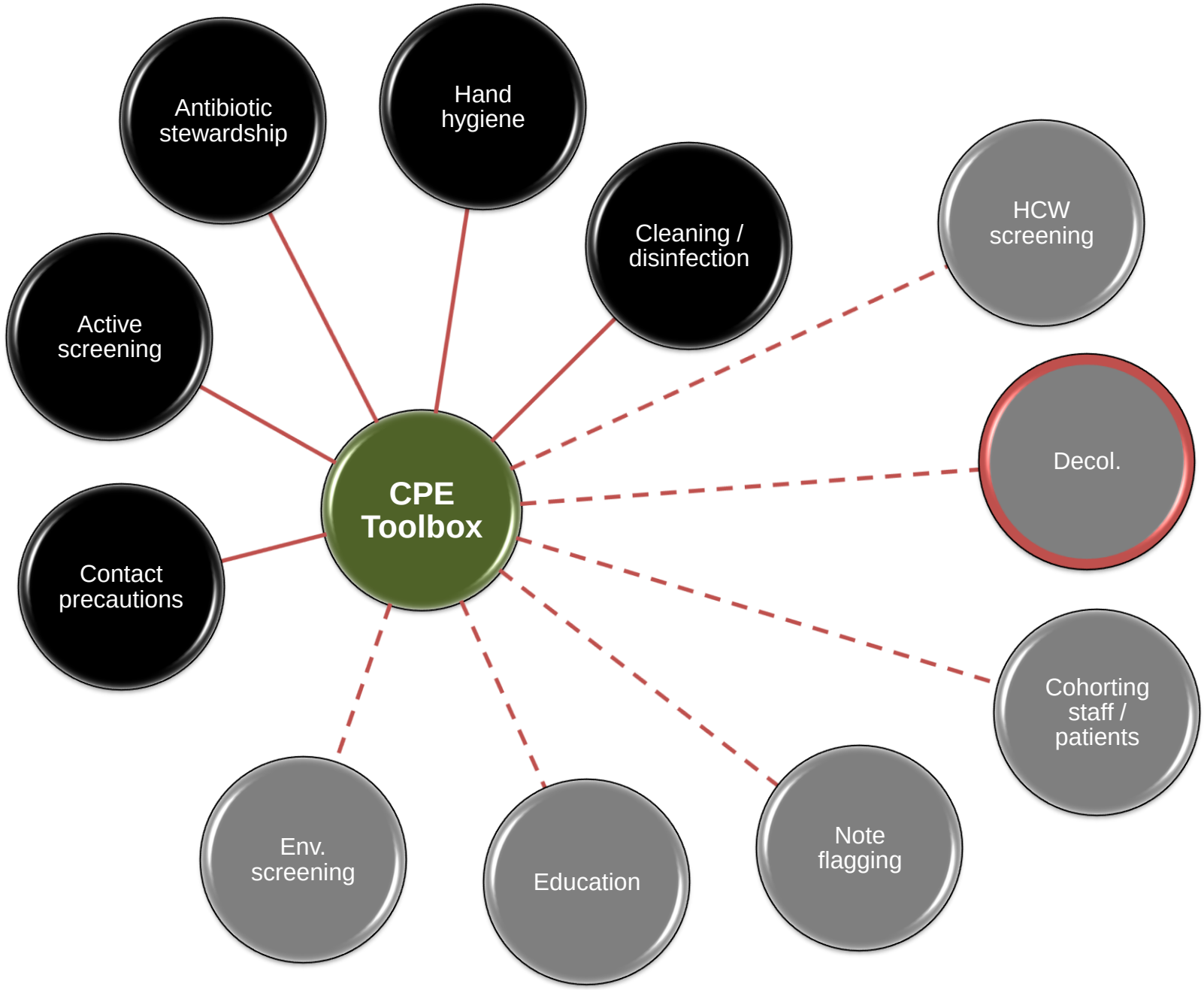
Gharbi *et al*. *Int J Antimicrob Agents* 2015 in press.

Antimicrobial stewardship – impact

Evaluating impact of 6 month antimicrobial stewardship intervention on an ICU by comparing bacterial resistance for matched 6 month periods either side of intervention.



Hou *et al. PLoS ONE* 2014;9:e101447; * = significant difference before vs. after.



Otter *et al. Clin Microbiol Infect* 2015 2015;21:1057–1066.

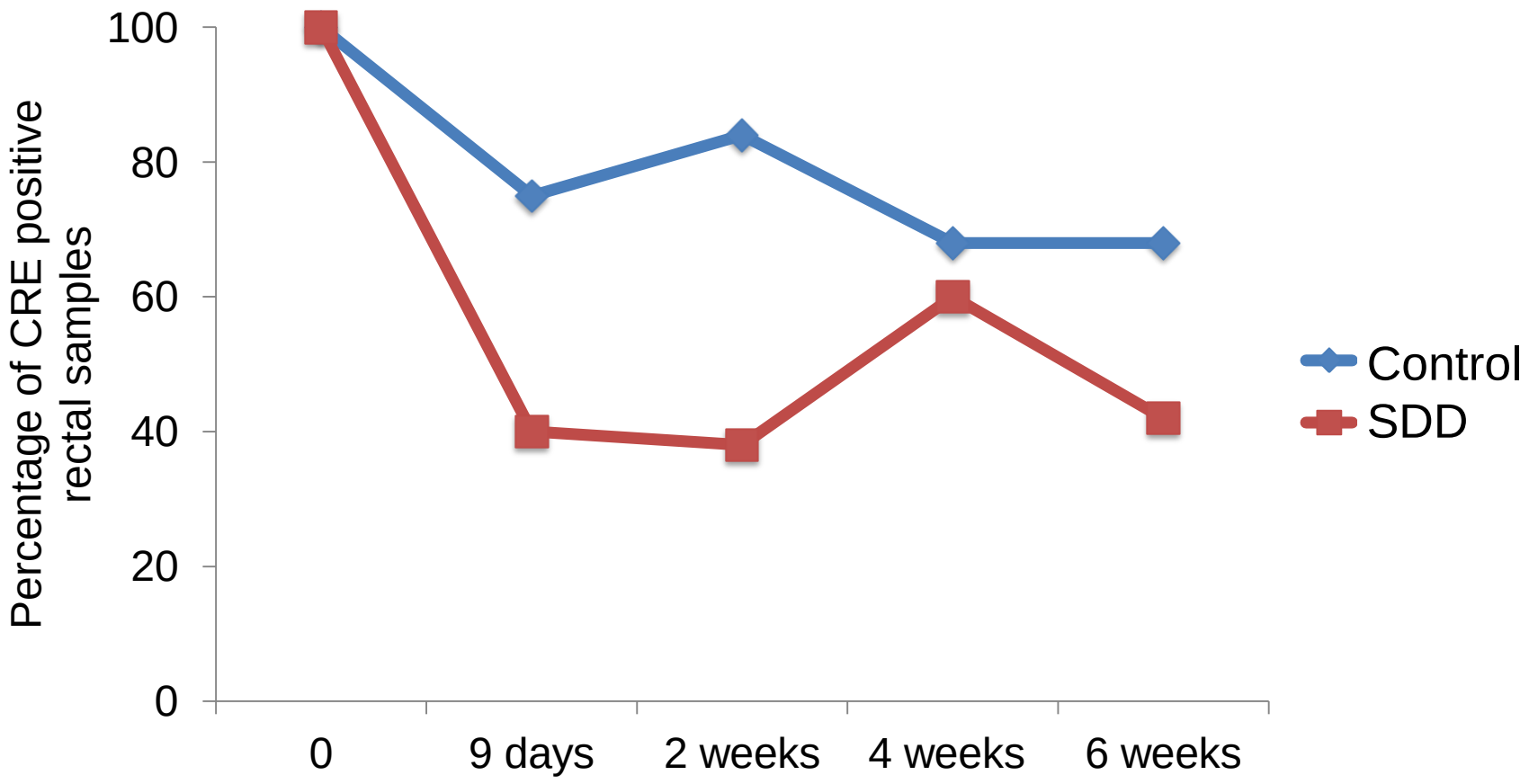
Deisolation?

Author	Year	Setting	N pts	Organism	Duration of colonization
Bird[1]	1998	Elderly care facilities, Scotland	38	ESBL *K. pneumoniae*	Mean 160 days (range 7-548)
Pacio[2]	2003	Long term care facility, USA	8	Resistant Gram-negative rods	Median 77 days (range 47-189)
Zahar[3]	2010	Paediatric hospital, France	62	ESBL Enterobacteriaceae	Median 132 days (range 65-228)
O'Fallon[4]	2009	Long term care facility, USA	33	Resistant Gram-negative rods	Median 144 days (range 41–349)
Zimmerman[5]	2013	Patients discharged from hospital, Israel	97	CRE	Mean 387 days

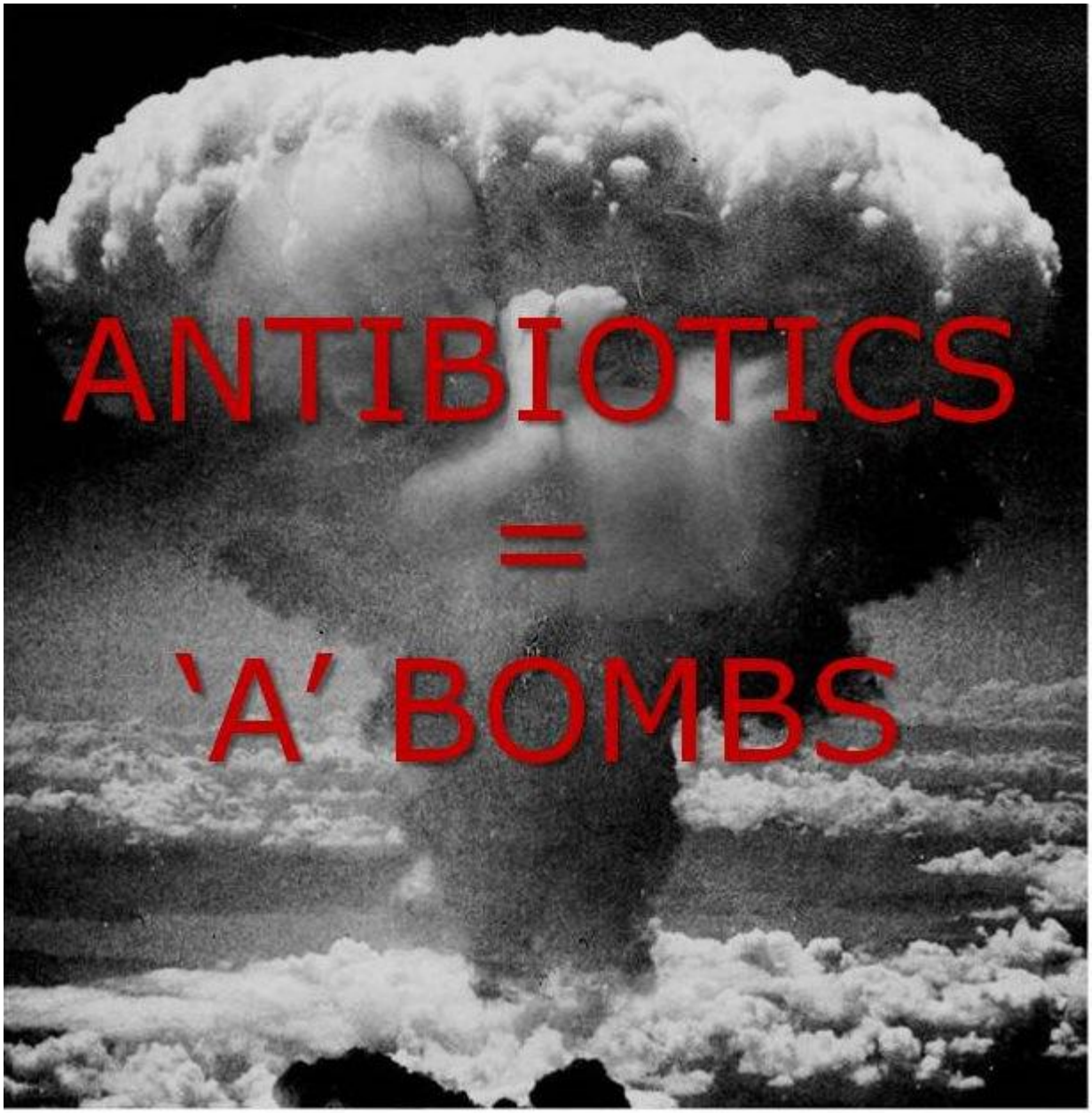
1. Bird *et al. J Hosp Infect* 1998;40:243-247.
2. Pacio *et al. Infect Control Hosp Epidemiol* 2003;24:246-250.
3. Zahar *et al. J Hosp Infect* 2010;75:76-78.
4. O'Fallon *et al. Clin Infect Dis* 2009;48:1375-1381.
5. Zimmerman *et al. Am J Infect Control* 2013;41:190-194.

‘Selective’ digestive decontamination

20 CRE colonized patients in each arm given gentamicin + polymyxin (SDD arm) or placebo (Control arm)



Saidel-Odes *et al. Infect Control Hosp Epidemiol* 2012;33:14-19.


ANTIBIOTICS
=
'A' BOMBS

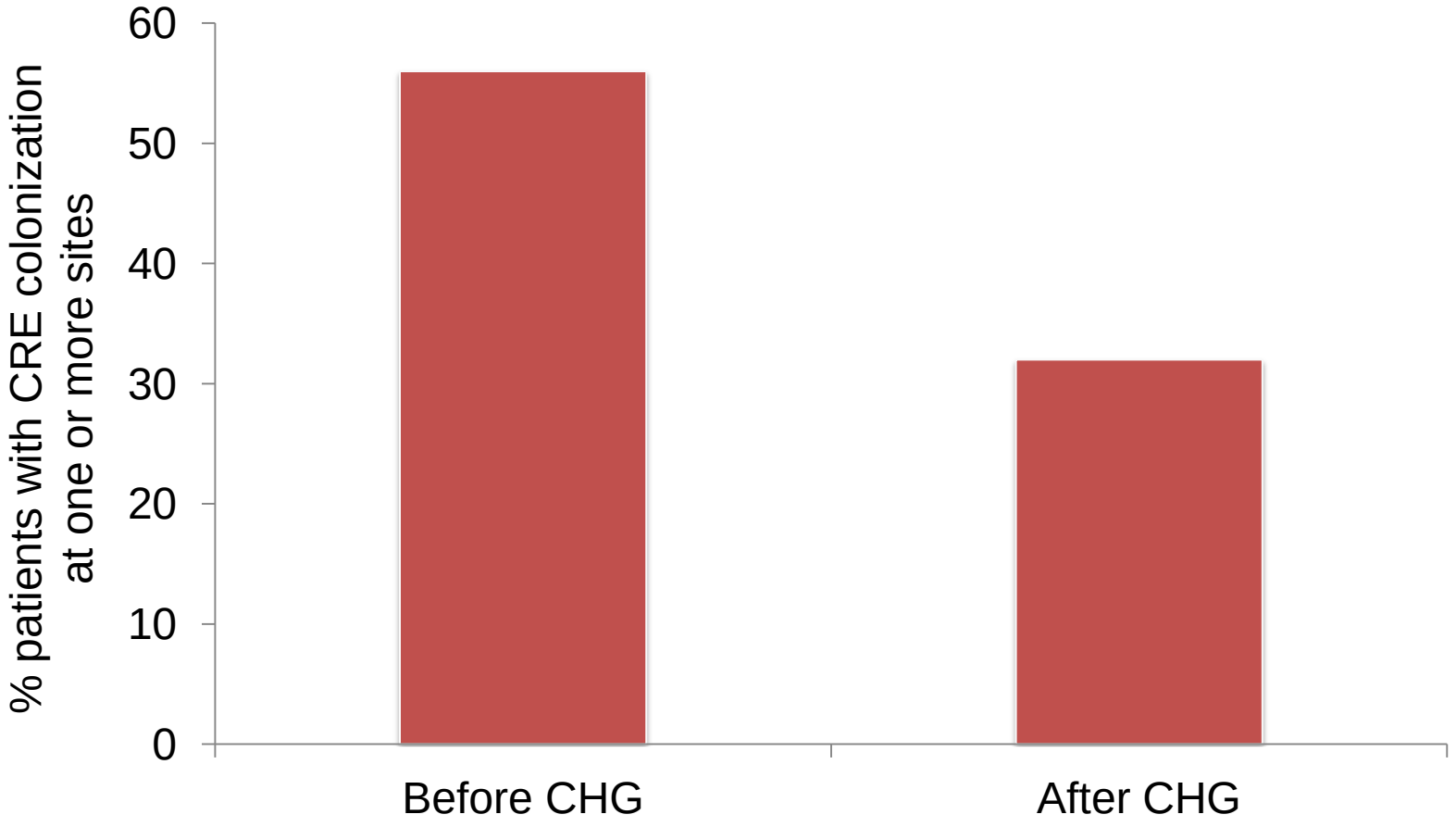
Decolonisation using faecal microbiota transplantation (FMT)

- 82 year old colonised with CPE.
- Carriage was delaying her admission to a nursing home.
- Single dose of FMT decolonised her at 7 and 14 days.

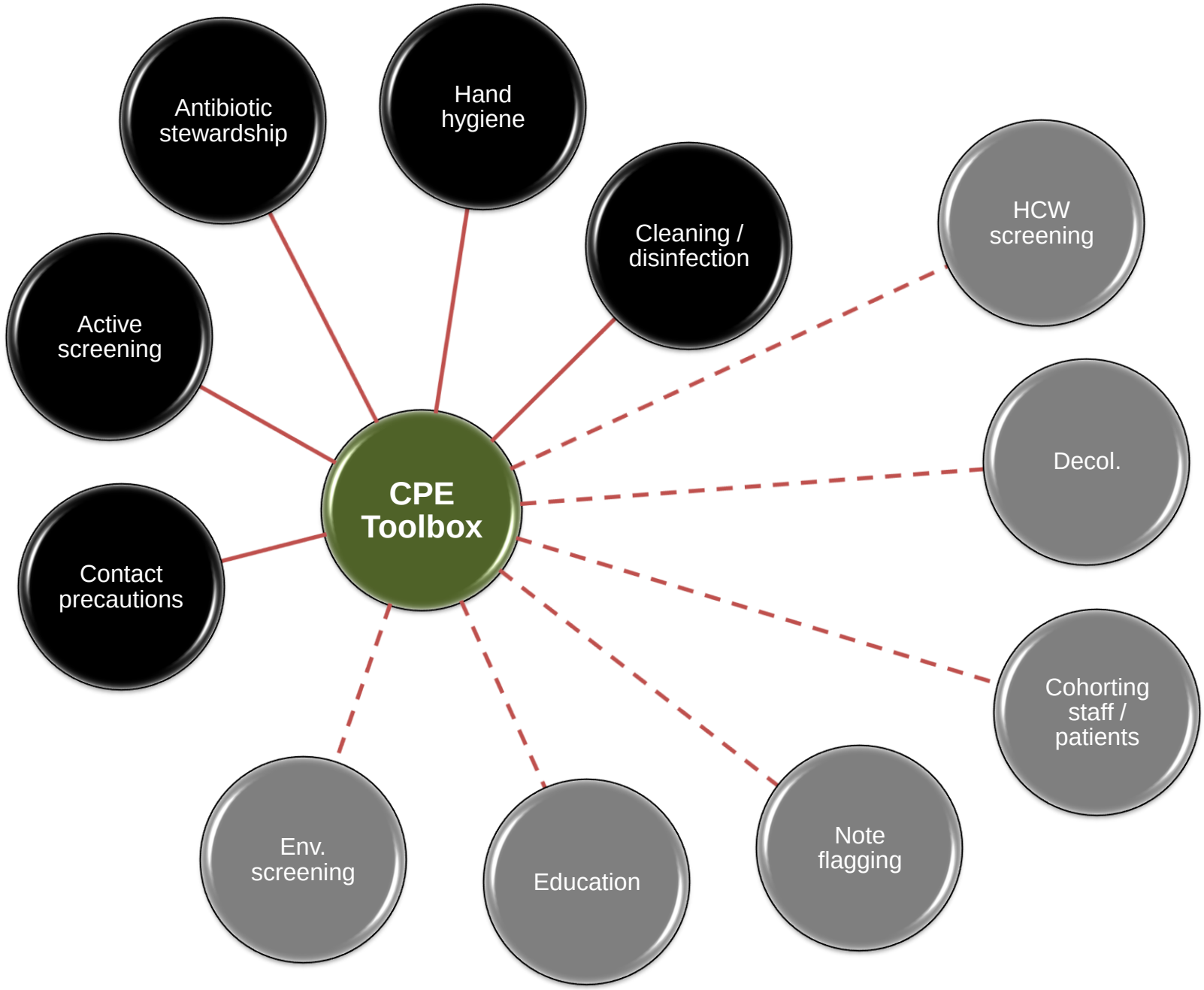
Laiger *et al. J Hosp Infect* 2015 in press.
Buffie & Pamer. *Nat Rev Microbiol* 2013;13:790-801.

Chlorhexidine – efficacy

Impact of chlorhexidine gluconate (CHG) daily bathing on skin colonization with KPC-producing *K. pneumoniae* in 64 long-term acute care patients.

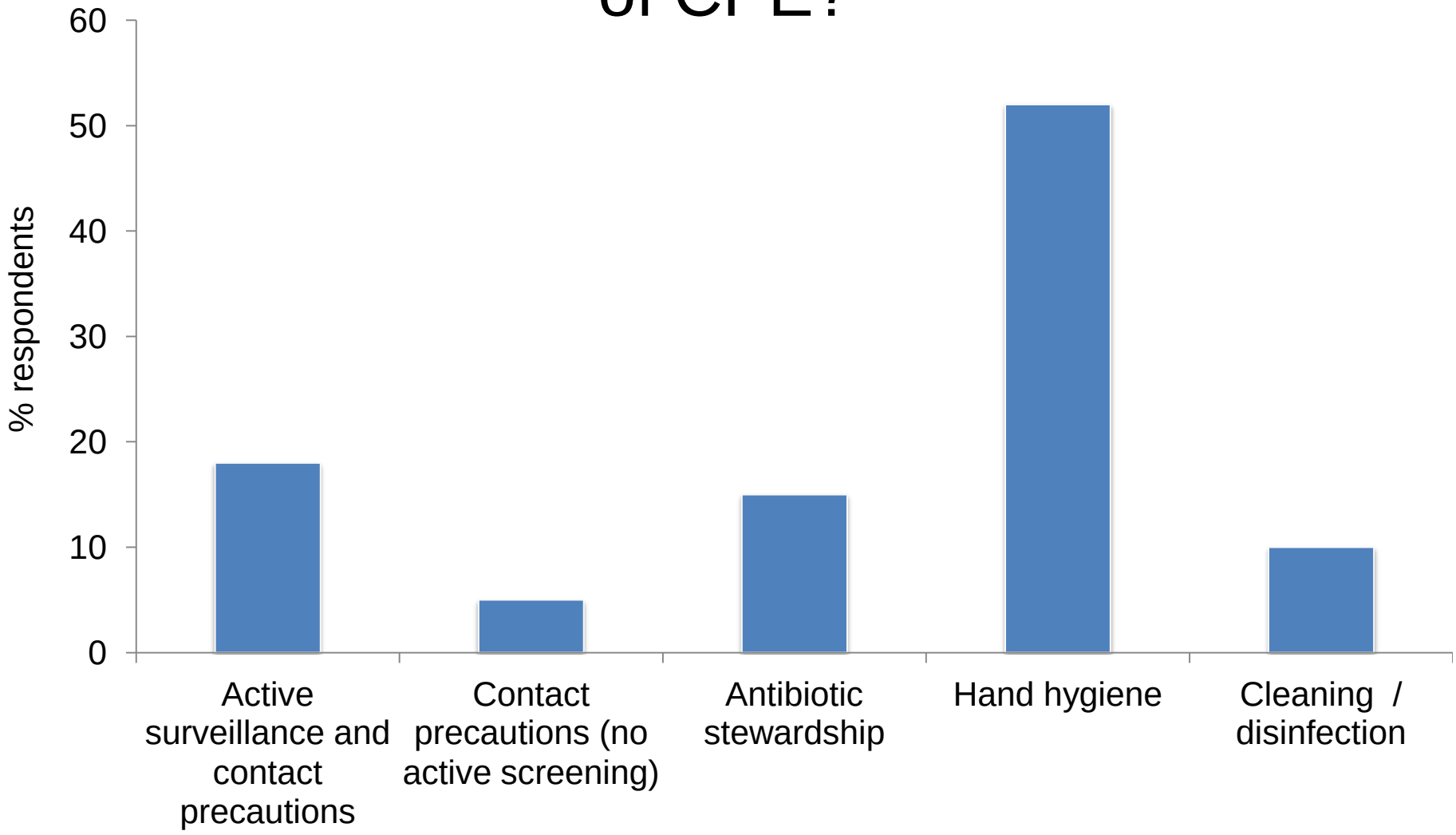


Lin *et al. Infect Control Hosp Epidemiol* 2014; 35:440-442.



Otter *et al. Clin Microbiol Infect* 2015 2015;21:1057–1066.

Which do you consider to be the most important measure to prevent transmission of CPE?



Data from around 150 webinar participants, mainly in the US, 2014.

Summary 1

1. CPE combine resistance, virulence and the potential for rapid spread.
2. Prevalence in the US and Europe appears to be patchy, but increasing; rates in parts of S. Europe are high.
3. We do not yet know what is effective in terms of prevention and control, but screening and isolation of carriers seems prudent.
4. Inter species resistance determinant transmission in the gut an increasing concern

Summary 2

- Vigilance, suspicion
- Isolation, screening, follow up,
- Hand hygiene, cleaning, decontamination
- Once positive……
- Aggressive dual/triple agent Rx
- Source control
- Antimicrobial stewardship

Thanks

- Jon Otter
- Frances Davies
- Alison Holmes
- Mark Gilchrist
- Eimear Brannigan
- IPC team @ imperial