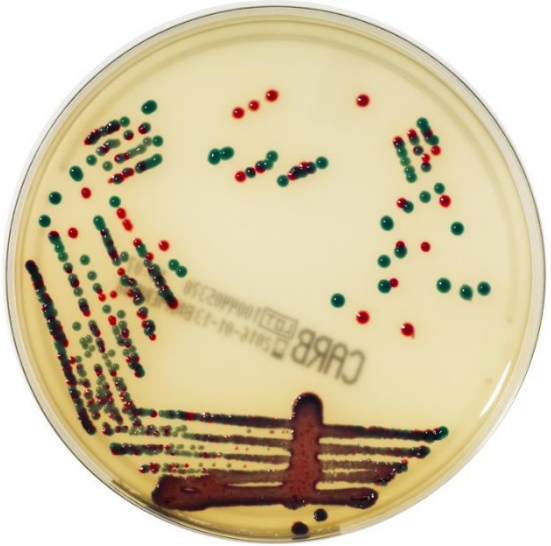
The rising threat from carbapenem-resistant organisms, and how to control them



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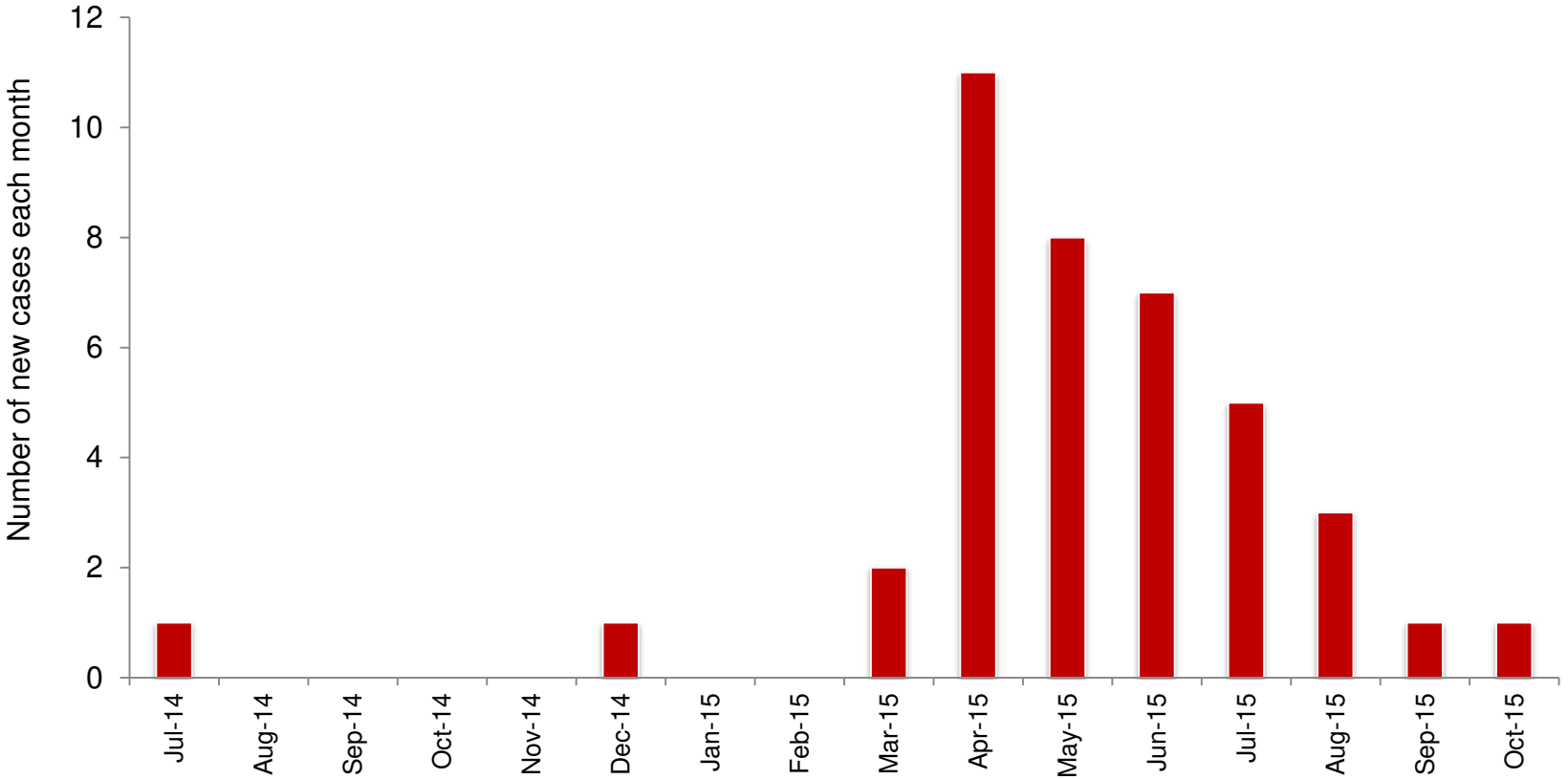
NHS
Guy's and St Thomas'
NHS Foundation Trust

Q1. Please rank the following as threats to our hospitals

- CPE
- MRSA
- C. difficile
- COVID-19

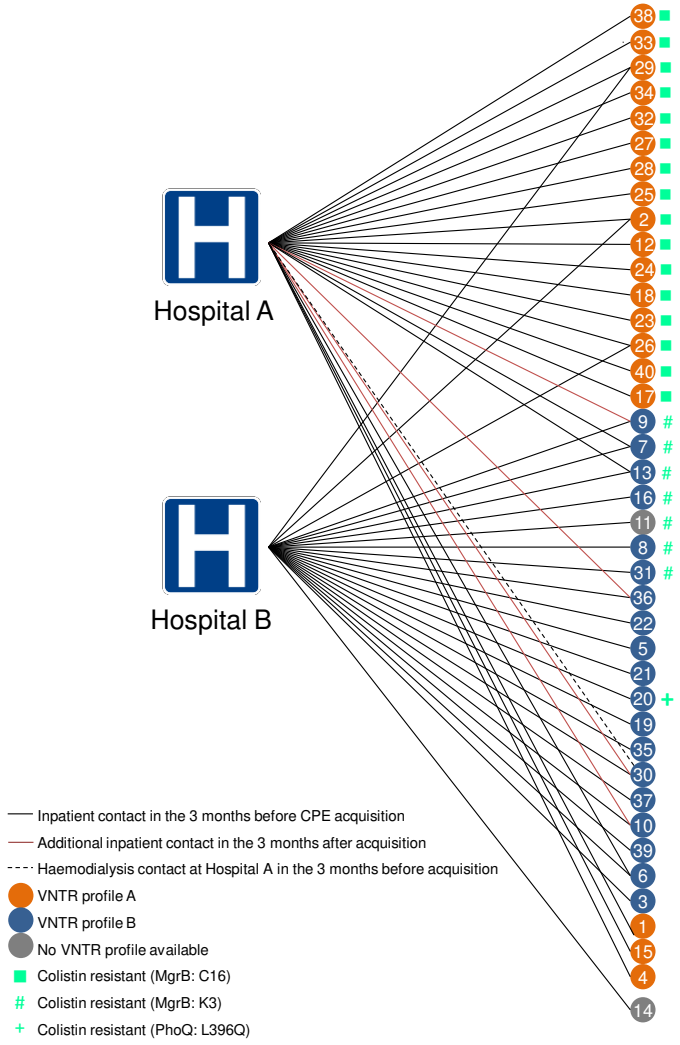
CPE outbreak @ Imperial (*K. pneumoniae* NDM)

8 cases first identified by clinical culture, 32 by screening culture; of these 32, 14 had a subsequent positive clinical culture



Otter *et al. Sci Rep* 2017;7:12711.

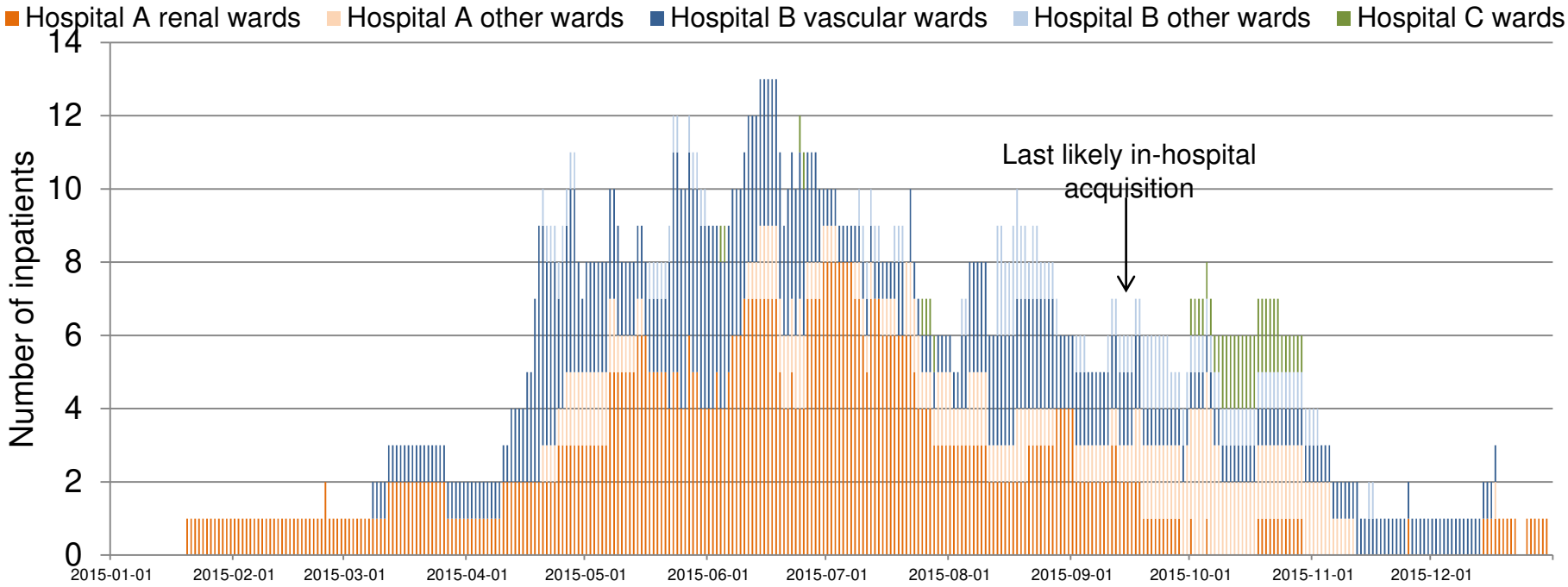
Emergence of colistin resistance



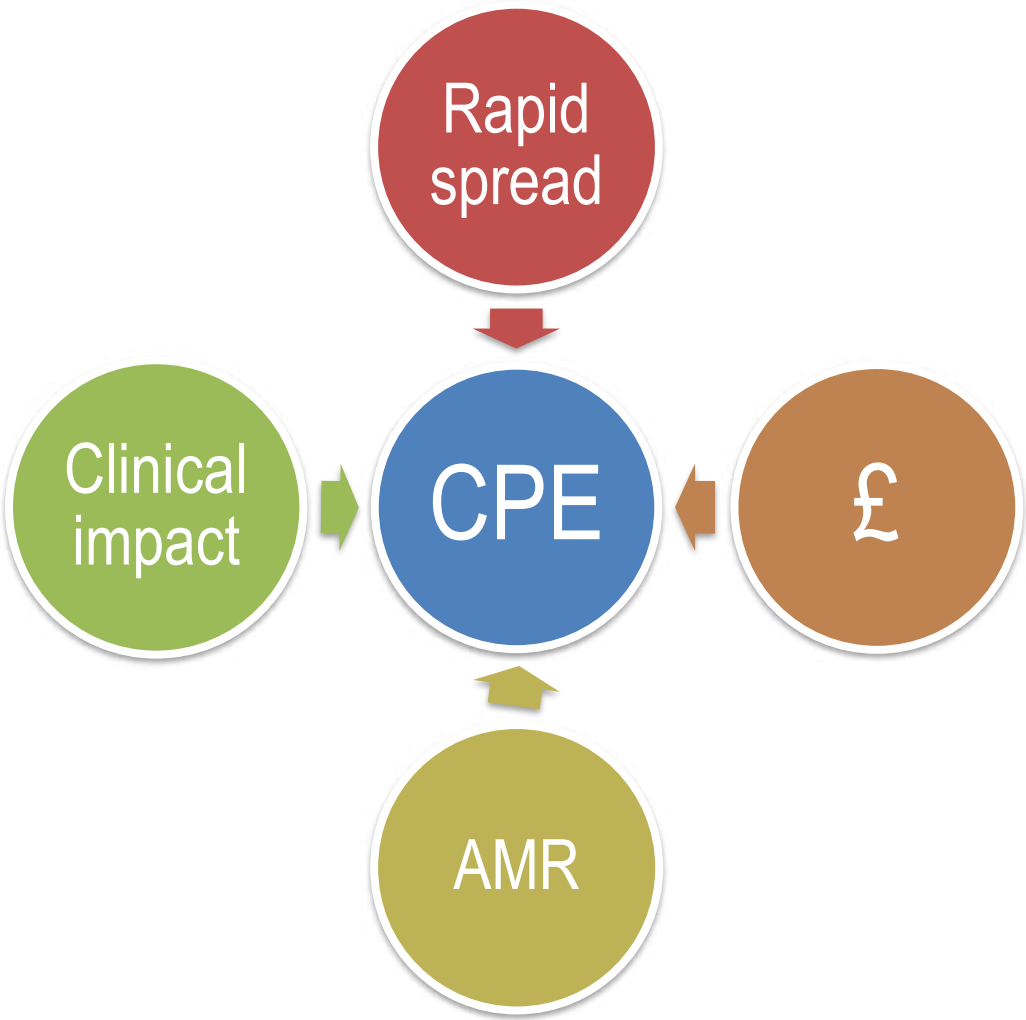
Otter *et al. Sci Rep* 2017;7:12711.

Contact precautions

The number of inpatients with known CPE carriage, daily

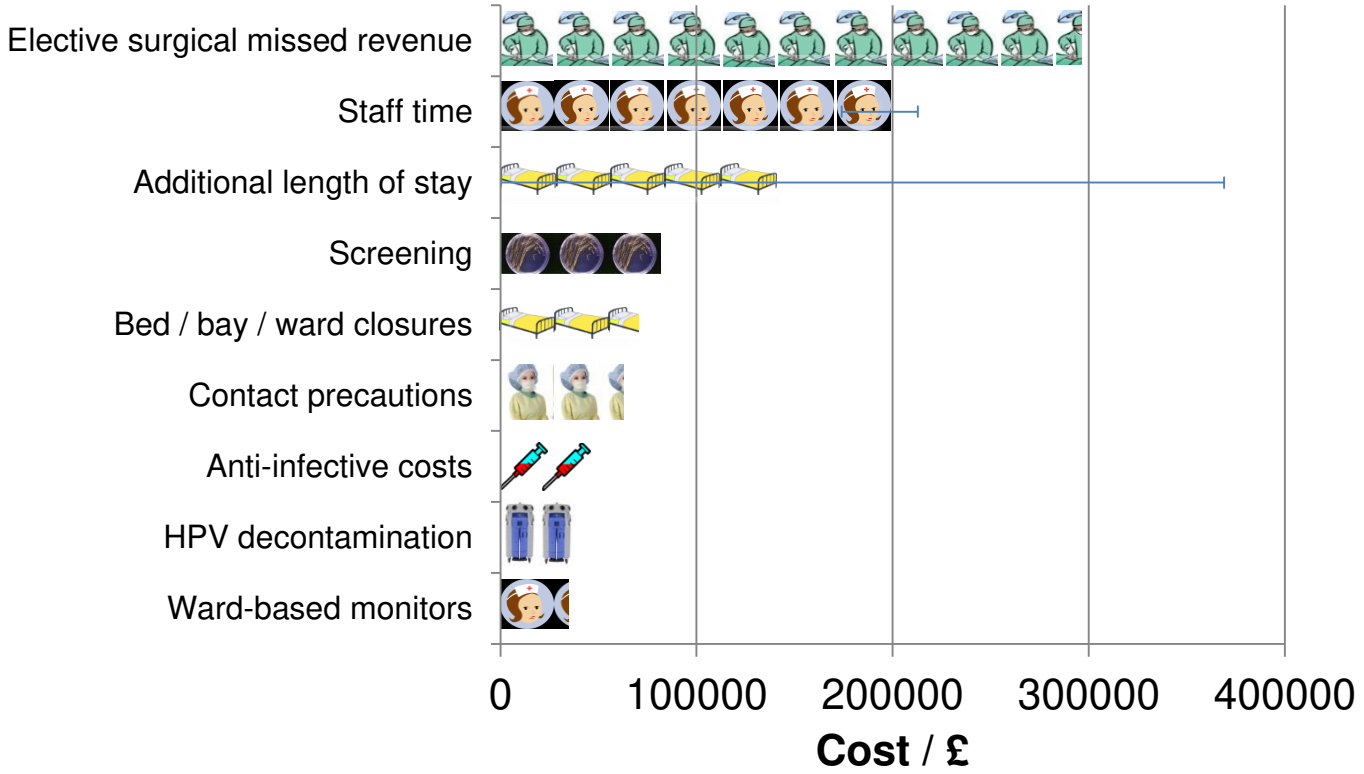


1831 contact precautions days generated, at a cost of £61,575 (£37,389 in gloves and aprons, £23,588 in stock disposal, and £598 in infectious waste disposal)


Rapid spread
Clinical impact
CPE
£
AMR

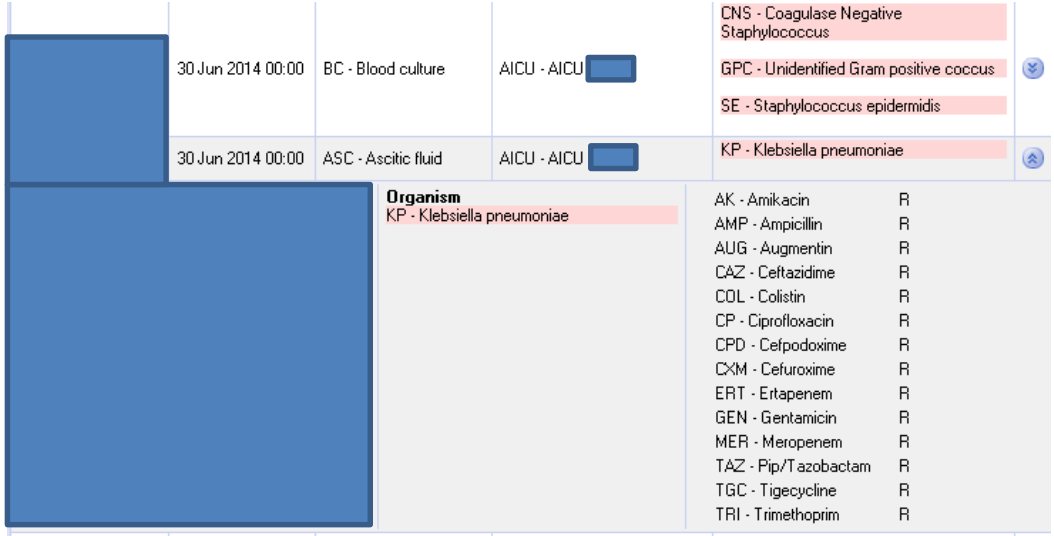
What's the problem? ££££

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



Otter *et al. Clin Microbiol Infect* 2016.

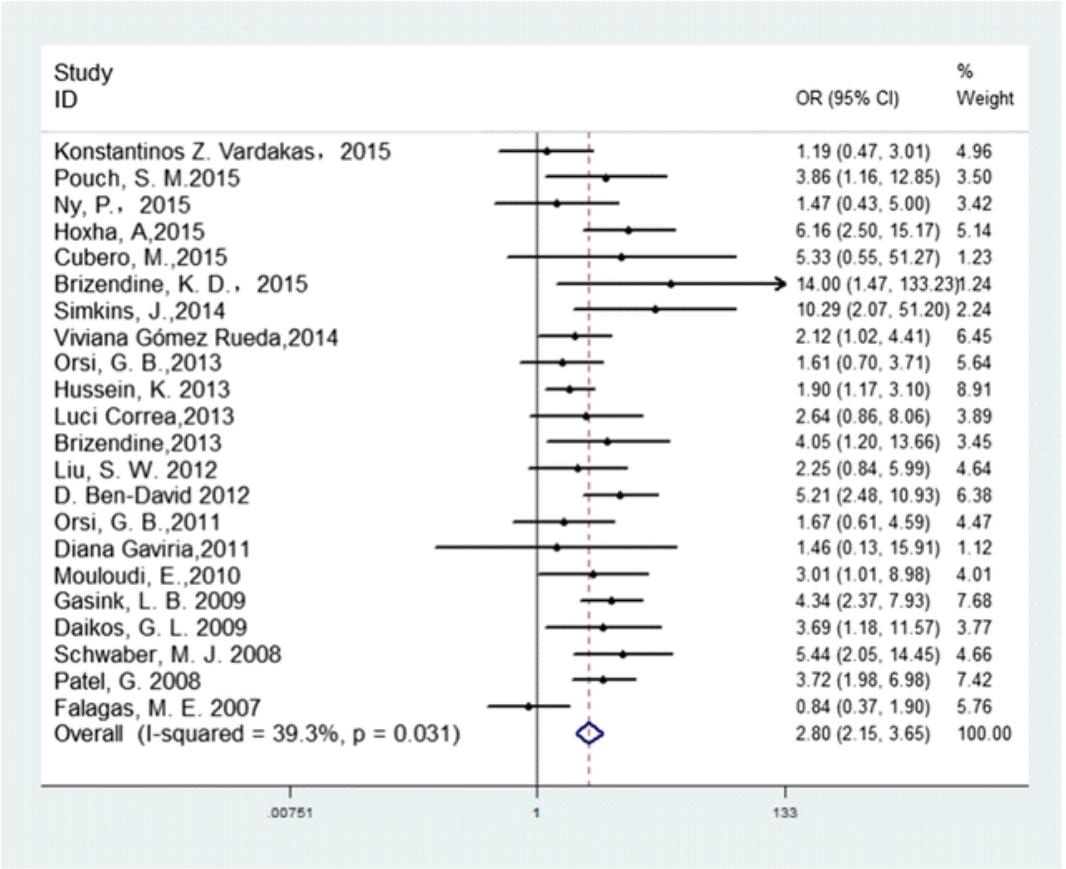
What's the problem? Resistance



[redacted]	30 Jun 2014 00:00	BC - Blood culture	AICU - AICU [redacted]	CNS - Coagulase Negative Staphylococcus GPC - Unidentified Gram positive coccus SE - Staphylococcus epidermidis
	30 Jun 2014 00:00	ASC - Ascitic fluid	AICU - AICU [redacted]	KP - Klebsiella pneumoniae

[redacted]	Organism		
	KP - Klebsiella pneumoniae	AK - Amikacin	R
		AMP - Ampicillin	R
		AUG - Augmentin	R
		CAZ - Ceftazidime	R
		COL - Colistin	R
		CP - Ciprofloxacin	R
		CPD - Cefpodoxime	R
		CXM - Cefuroxime	R
		ERT - Ertapenem	R
		GEN - Gentamicin	R
		MER - Meropenem	R
		TAZ - Pip/Tazobactam	R
		TGC - Tigecycline	R
		TRI - Trimethoprim	R

What's the problem? Mortality



Crude odds ratio (OR) for the association between carbapenem resistance and mortality of patients with *K. pneumoniae* infection

Xu et al. Annal Clin Microbiol Antimicrob 2017.

Carbapenem-resistant bloodstream infection is really bad news in ICU – and not all CPE are equal

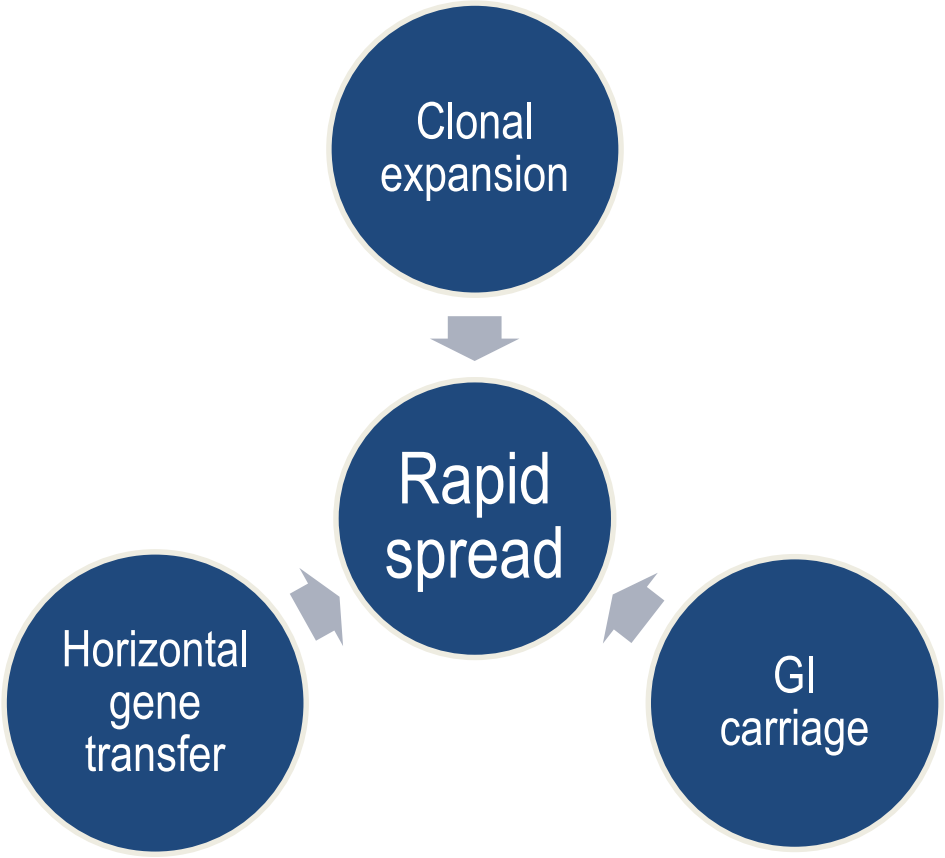
Retrospective observational study from 19 Italian hospitals between 2018 and 2020. A total of 1276 monoclonal Gram-negative BSIs were included (polymicrobial BSIs were excluded). 30% (!) of these ICU-associated BSIs were CPE.

Carbapenam-resistant Gram negative bacilli	**Crude 30-Day Mortality**	**Adjusted Odds Ratio of Death**	**Attributable Mortality, Controls: Patients With Carbapenem-Susceptible Bloodstream Infection**
KPC–producing Enterobacterales	26.5%	1.43 (0.92–2.22)	5%
MBL*–producing Enterobacterales	36.4%	5.86 (2.72–12.76)	35%
CR *Pseudomonas aeruginosa*	32.8%	2.99 (1.48–5.95)	19%
CR *Acinetobacter baumannii*	43.2%	2.65 (1.52–4.61)	16%

MBLs* include NDM, VIM, and IMP carbapenemases

Falcone et al. Clin Infect Dis 2023.

What's the problem? Rapid spread



Rising threat from multidrug-resistant Gram-negative bacteria

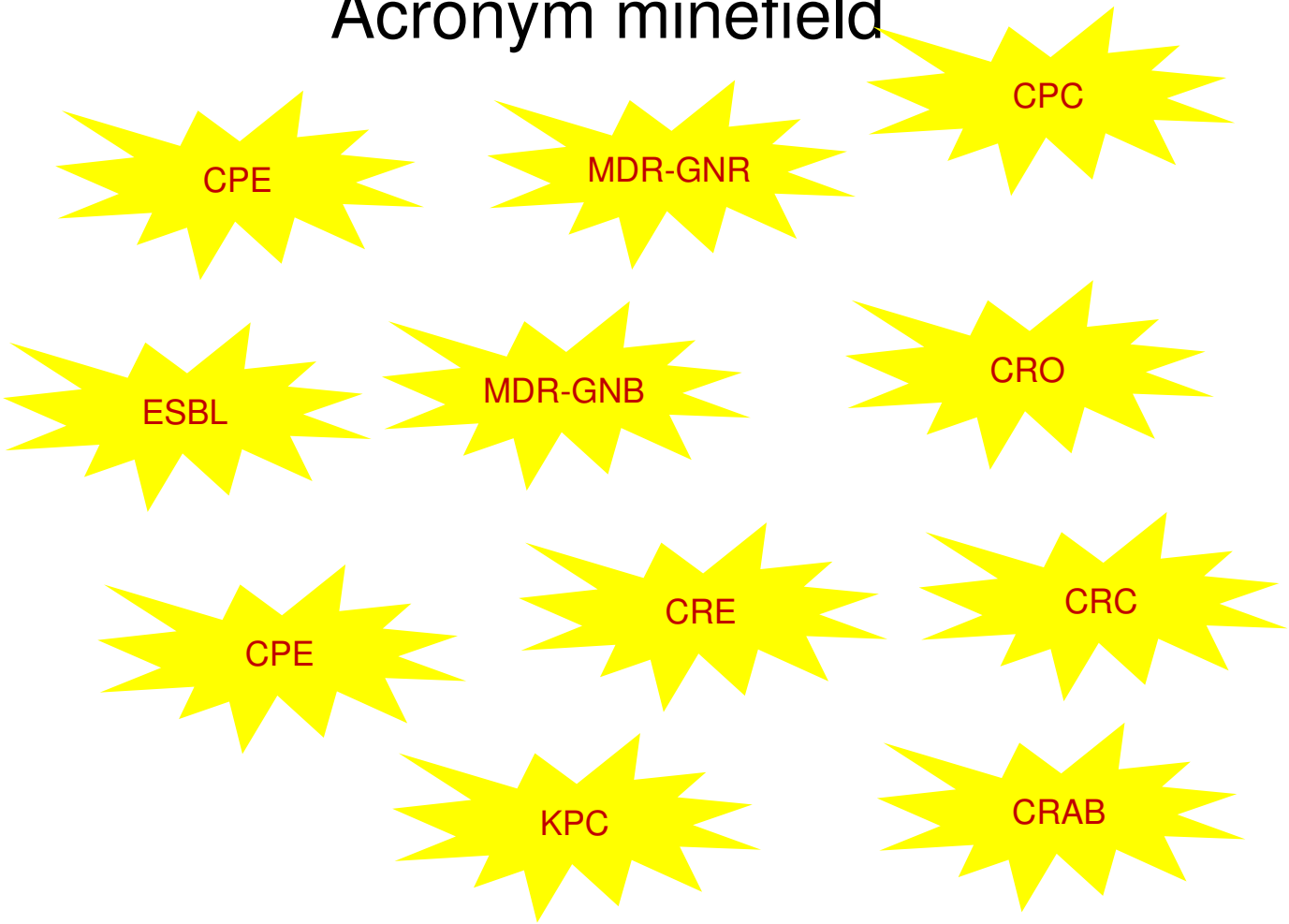
% of all HAI caused by GNRs.

% of ICU HAI caused by GNRs.

Non-fermenters	***Acinetobacter baumannii*** ***Pseudomonas aeruginosa*** ***Stenotrophomonas maltophilia***	**CPO**
Enterbacterales	*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.

Acronym minefield

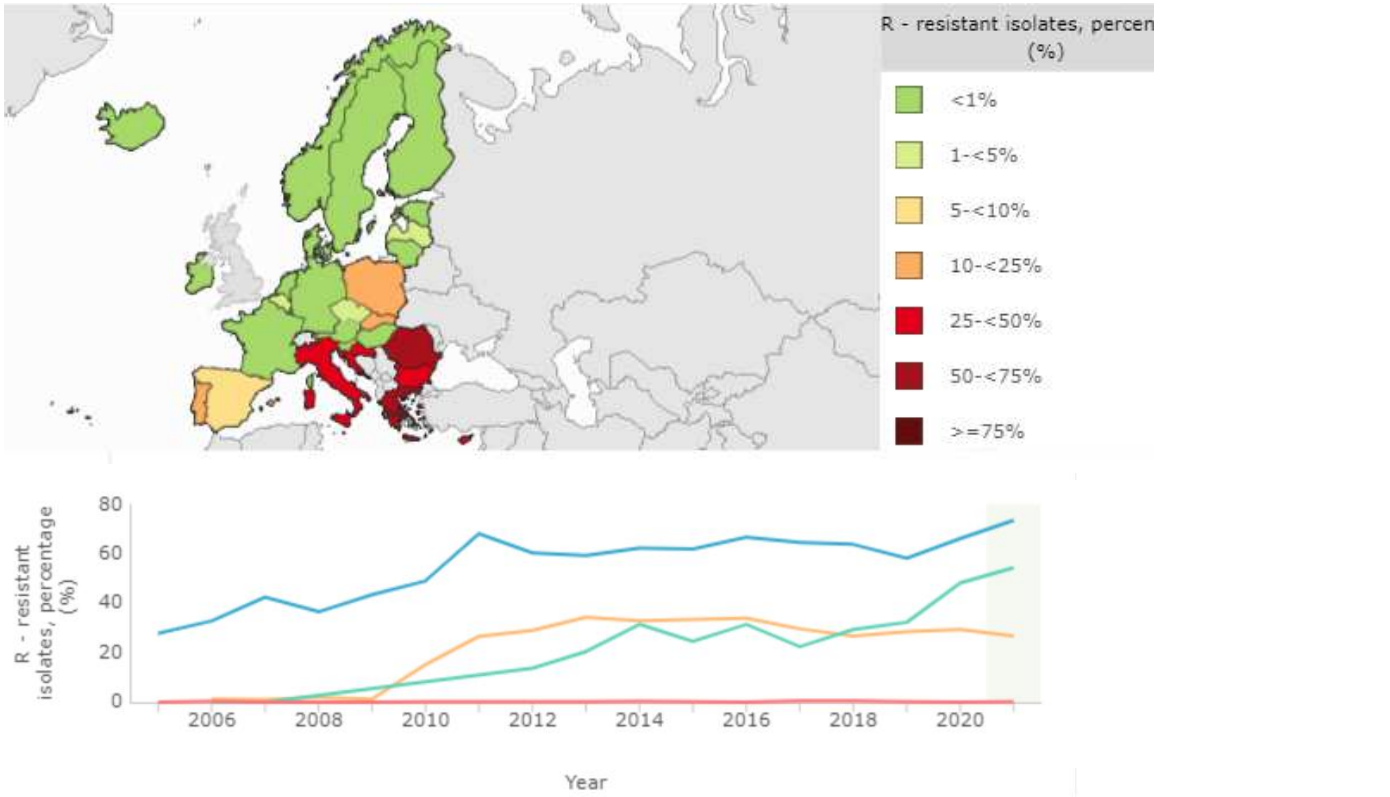


The emerging threat of CPE

Pathogen	CPE	MRSA	VRE	*C. difficile*
Resistance	+++	+	+	+/-
Resistance genes	Multiple	Single	Single	n/a
Species	Multiple	Single	Single	Single
HA vs CA	HA & CA	HA	HA	HA
At-risk pts	All	Unwell	Unwell	Old
Virulence	+++	++	+/-	+
Environment	+/-	+	++	+++

CRE in Europe

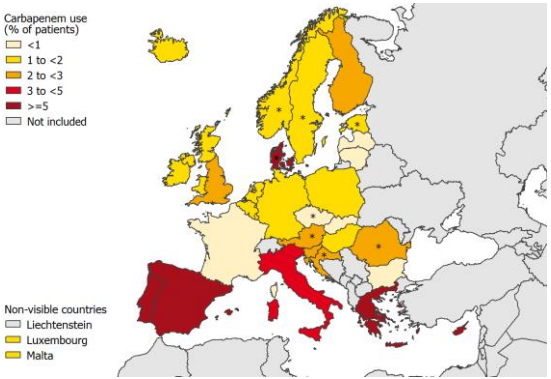
% invasive K. pneumoniae isolates resistant to carbapenems



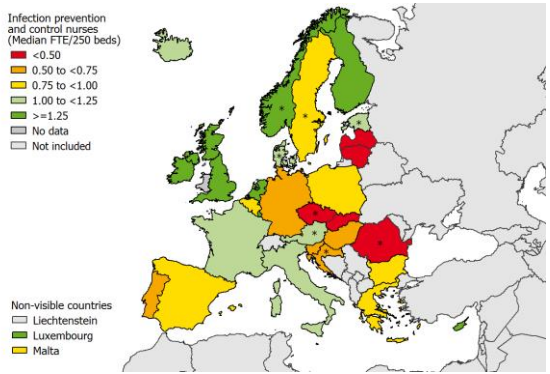
ECDC 2023.

What drives the European ‘north-south divide’?

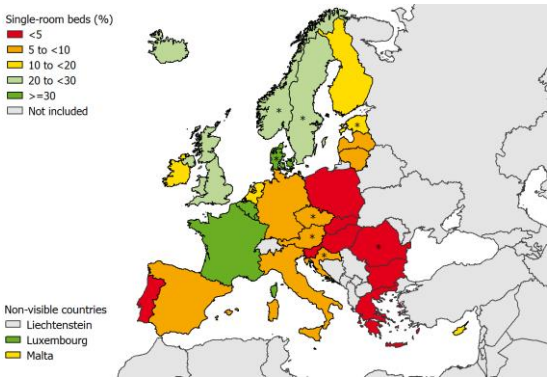
Antibiotic use



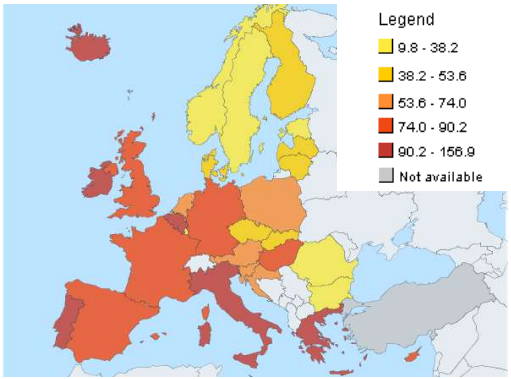
Infection control staffing



Single room availability



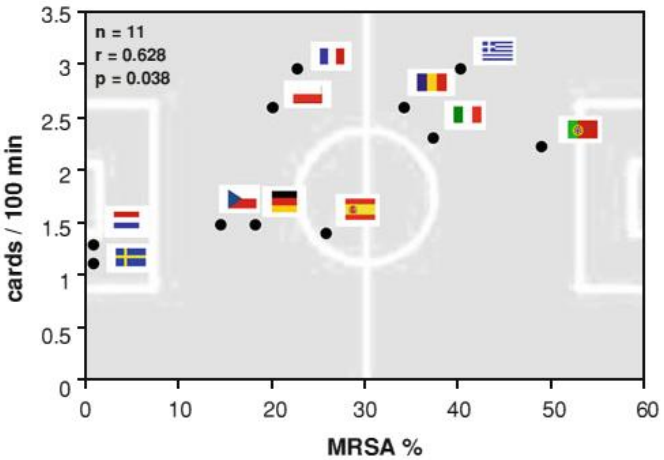
National debt



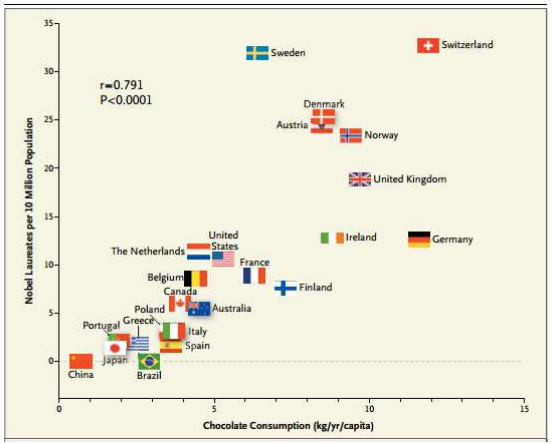
1. ECDC Point Prevalence Survey, 2013.
2, National debt as a percentage of GDP. "Eurostat public debt GDP" by Eurostat. Licensed under Attribution via Wikimedia Commons.

What drives the European ‘north-south divide’?

Correlation between MRSA rate in BSIs and an indicator for fair play from the European Football Championships (red or yellow cards / 100 min)[1]



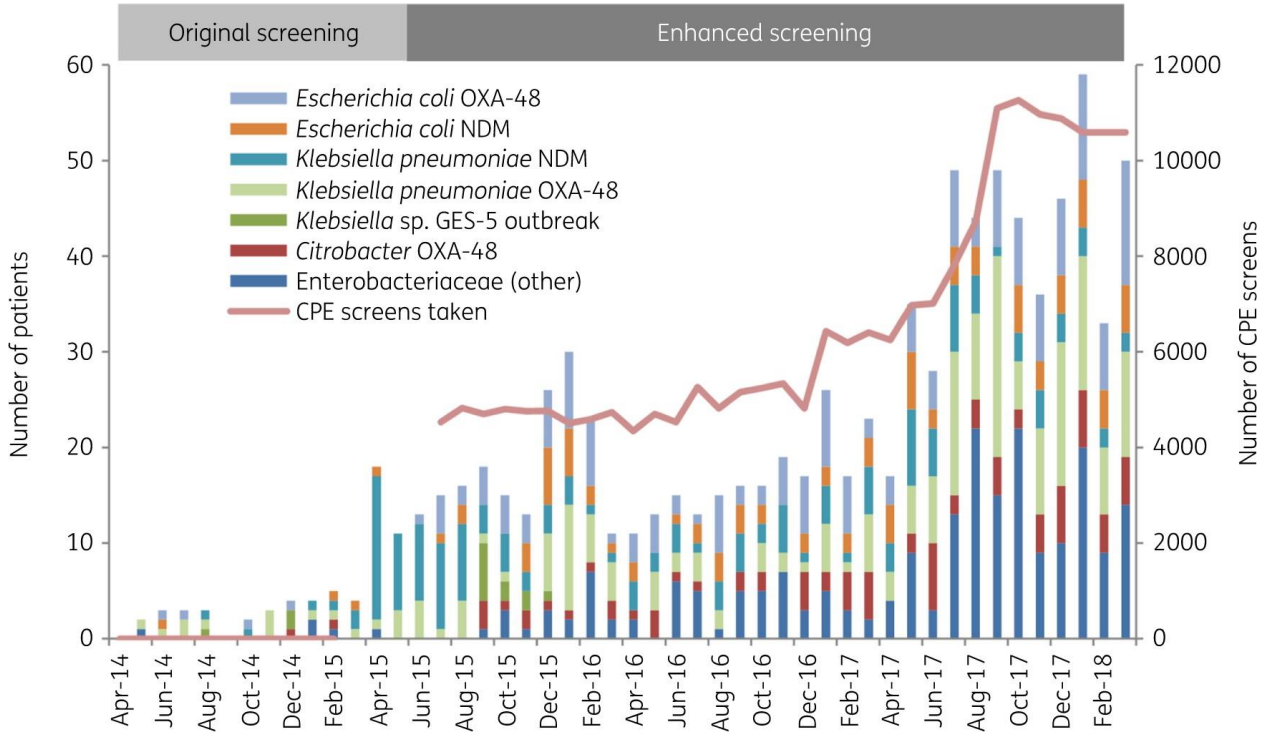
Correlation between national chocolate consumption and rate of Nobel prize winners.[2]



1. Meyer *et al. Infection* 2012 in press.
2. Messerli FH. *New Engl J Med* 2012;367:1562-4.

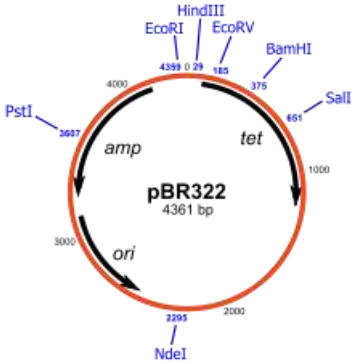
Seek and ye shall find…

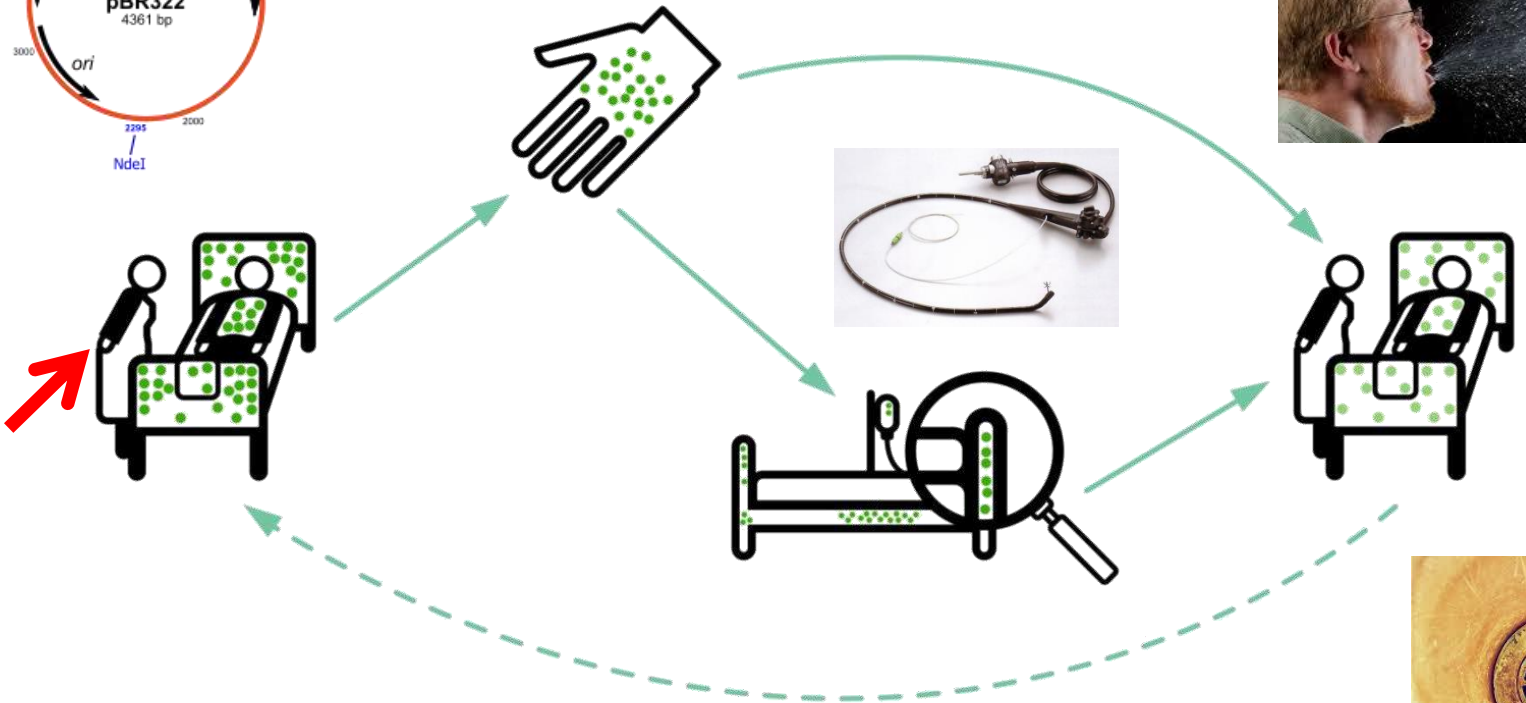
Overall trend in CPE detected at the Trust, by bacterial species and mechanisms, deduplicated by patient



Otter et al. J Antimicrob Chemother 2020.

Transmission modes



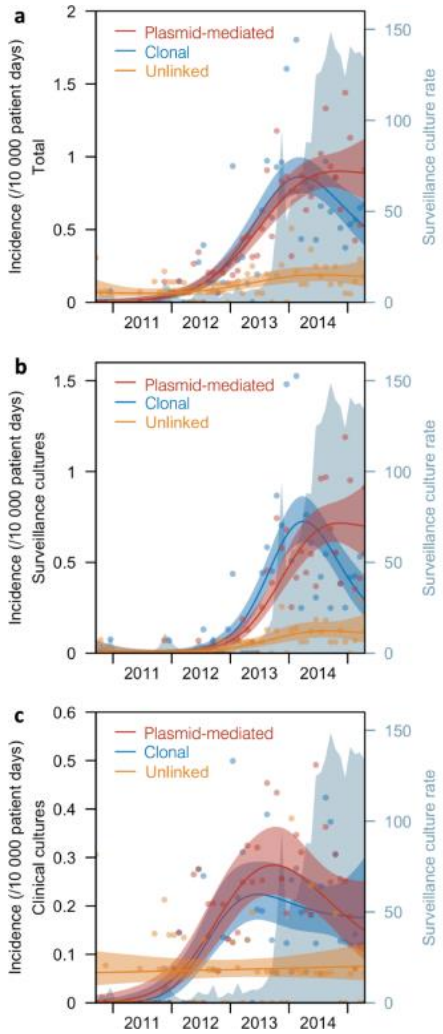


Otter *et al. Infect Control Hosp Epidemiol* 2011;32:687-699.

Promiscuous plasmids

- Inter-species plasmid transfer of AMR genes was investigated in the 1970s regarding gentamicin-resistance.[1]
- There are several convincing individual small outbreaks where it is clear that inter-species plasmid transfer of AMR genes has occurred in Gram-negative bacteria.[2]
- In one plasmid outbreak,[3] multiple carbapenemases were dealt out like a pack of cards to multiple Enterobacterales species from a single index patient.
- More broadly, the population structure of KPC-producing *K. pneumoniae* is consistent with horizontal gene transfer.[4,5]
- **Need to look beyond 'same-organism-same-gene' transmission dynamics.**

1. Lee *et al. Antimicrob Agents Chemother* 1986;29(4):654-9.
2. Sheppard *et al. Antimicrob Agents Chemother* 2016;23:3767-78.
3. Hammerum *et al. J Antimicrob Chemother.* 2016;71:3117-3124.
4. Chen *et al. Trends Microbiol* 2014;22:686-96.
5. Doumith *et al. J Antimicrob Chemother* 2017;72:2241-2248.



Horizontal plasmid transfer is a key driver of CPE transmission

Genomic analysis of 1312 CPEs submitted to government ref lab in Singapore between 2010 and 2015.

Significant risk factors for clonal spread of CPE:

- direct or indirect ward-level contact;
- direct or indirect hospital-level contact;
- bacterial species (*Klebsiella* and *Enterobacter* a higher risk of spread than *E. coli;*
- carbapenemase type (NDM and OXA-type a higher risk of spread than KPC)

Significant risk factors for plasmid-mediated spread of CPE:

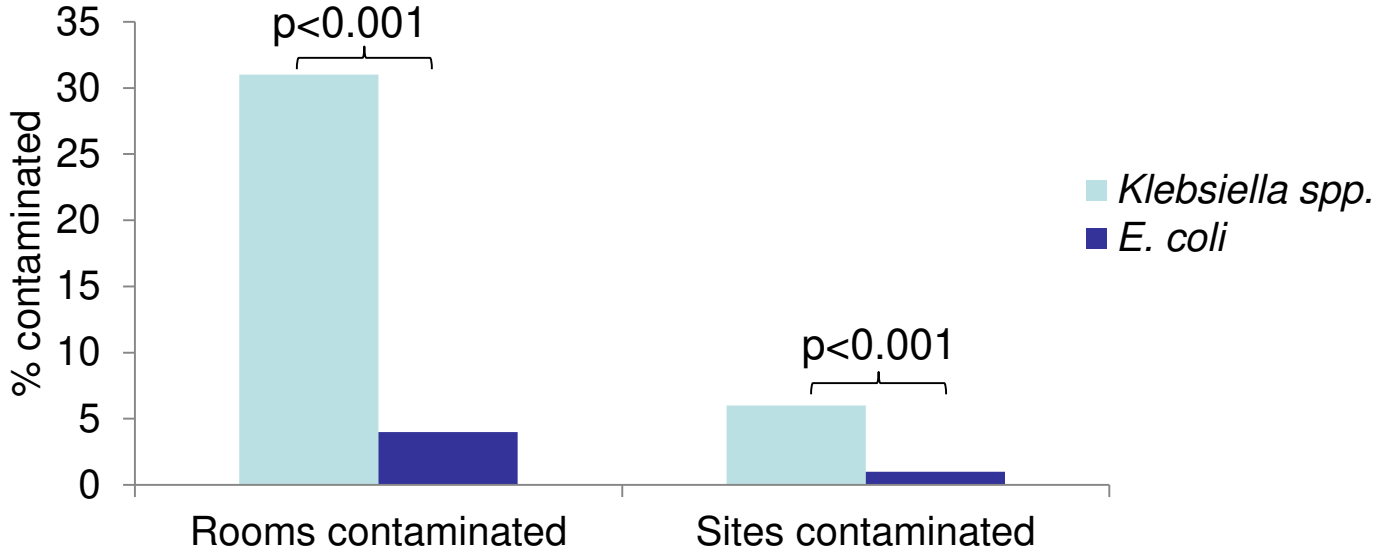
- **none**

Marimuthu et al. Nat Comm 2022.

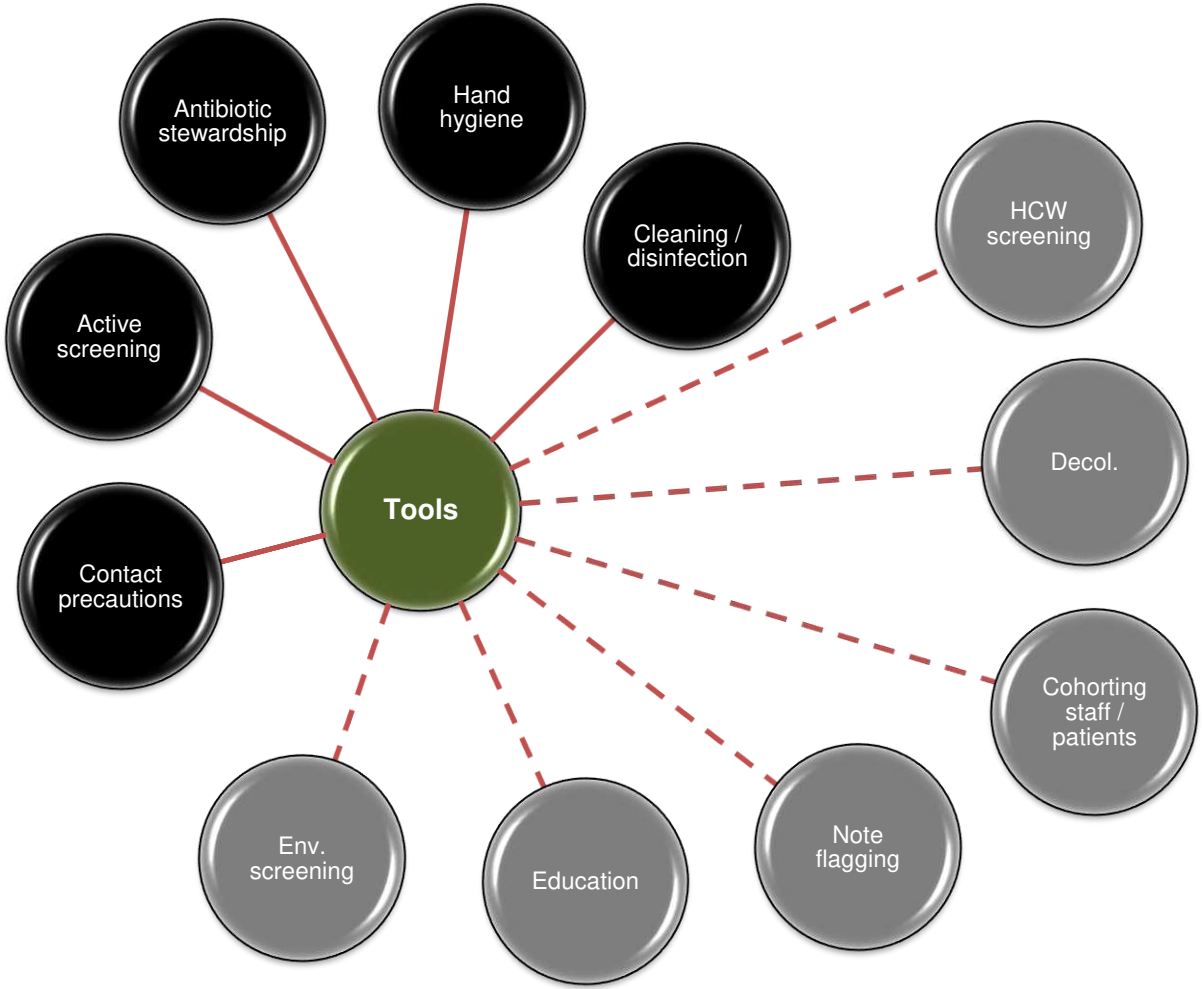
Transmissibility / fitness

- *Klebsiella* species **3.7x** more transmissible than *E. coli* in the ICU.[1]
- *K. pneumoniae* seems to be more environmental than *E. coli.*[2,3]

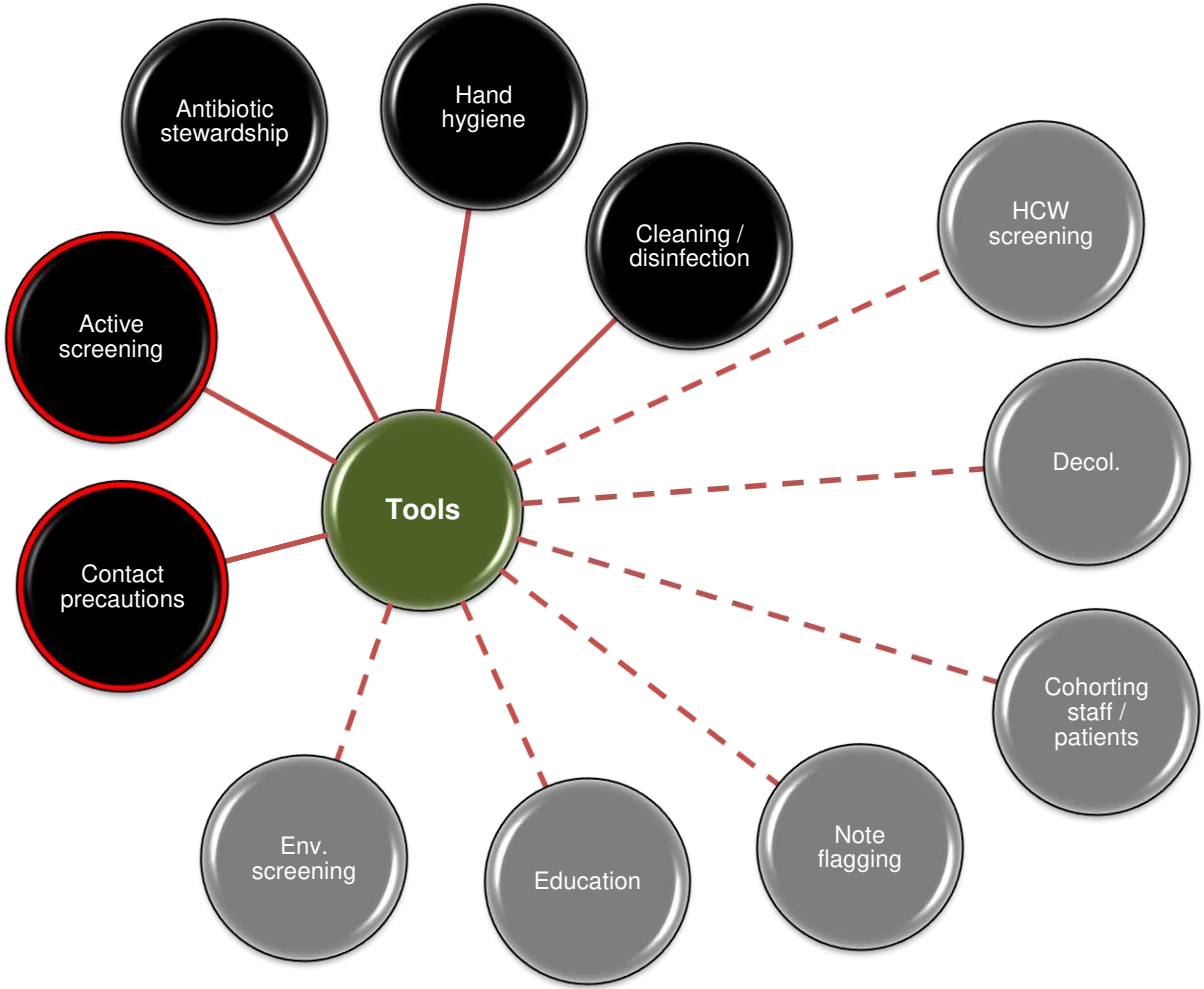
Surface contamination on five standardized sites surrounding patients infected or colonized with ESBL-producing *Klebsiella* spp. (n=48) or ESBL-producing *E. coli* (n=46).[2]



1. Gurieva *et al. Clin Infect Dis* 2018;66:489-93. 2. Guet-Revillet *et al. Am J Infect Control* 2012;40:845-8.
3. Gbaguidi-Haore. *Am J Infect Cont* 2013;41:664-5.



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



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

Q2. Who do you think should be screened on admission for CPO?

- All patients
- Everybody admitted to ICU
- Patients with a history of CPO
- Patients with an overnight hospital admission in the past 12 months
- Patients with a history of CPO OR with an overnight hospital admission in the past 12 months OR admitted to high-risk units

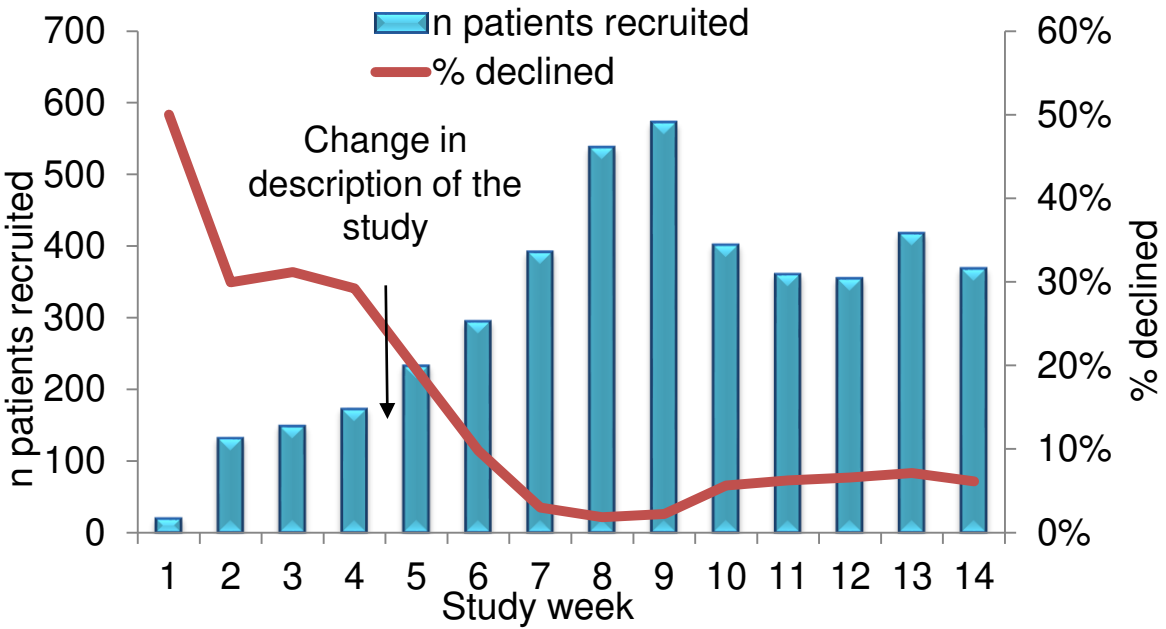
Who do I screen?

UKHSA Framework for CPE admission screening triggers, in the last 12 months, they have:

- been previously identified as CPE positive
- been an inpatient in any hospital, in the UK or abroad
- had multiple hospital treatments for example are dialysis dependent
- had known epidemiological link to a known carrier of CPE
- they are admitted into augmented care or high-risk units

Can I swab your rectum please?

Prospective study of asymptomatic antibiotic-resistant Gram-negative bacteria colonisation in 4006 patients on admission to a London hospital group.



Original description (weeks 1-4)

- "Bug"-focussed message
- Detailed scientific language

Modified description (weeks 5-14)

- Patient-focussed message
- "Why is it important to be screened?"
- "Benefits for you and those close to you!"
- "If you get an infection, we can put you on the right antibiotics straight away."

The change in study description results in a significant reduction in decline rate, from 31.9% of 869 patients to 7.6% of 3690 patients ($p < 0.001$)

Dyakova et al. Clin Microbiol Infect. 2017;23:577.e1-577.e3.

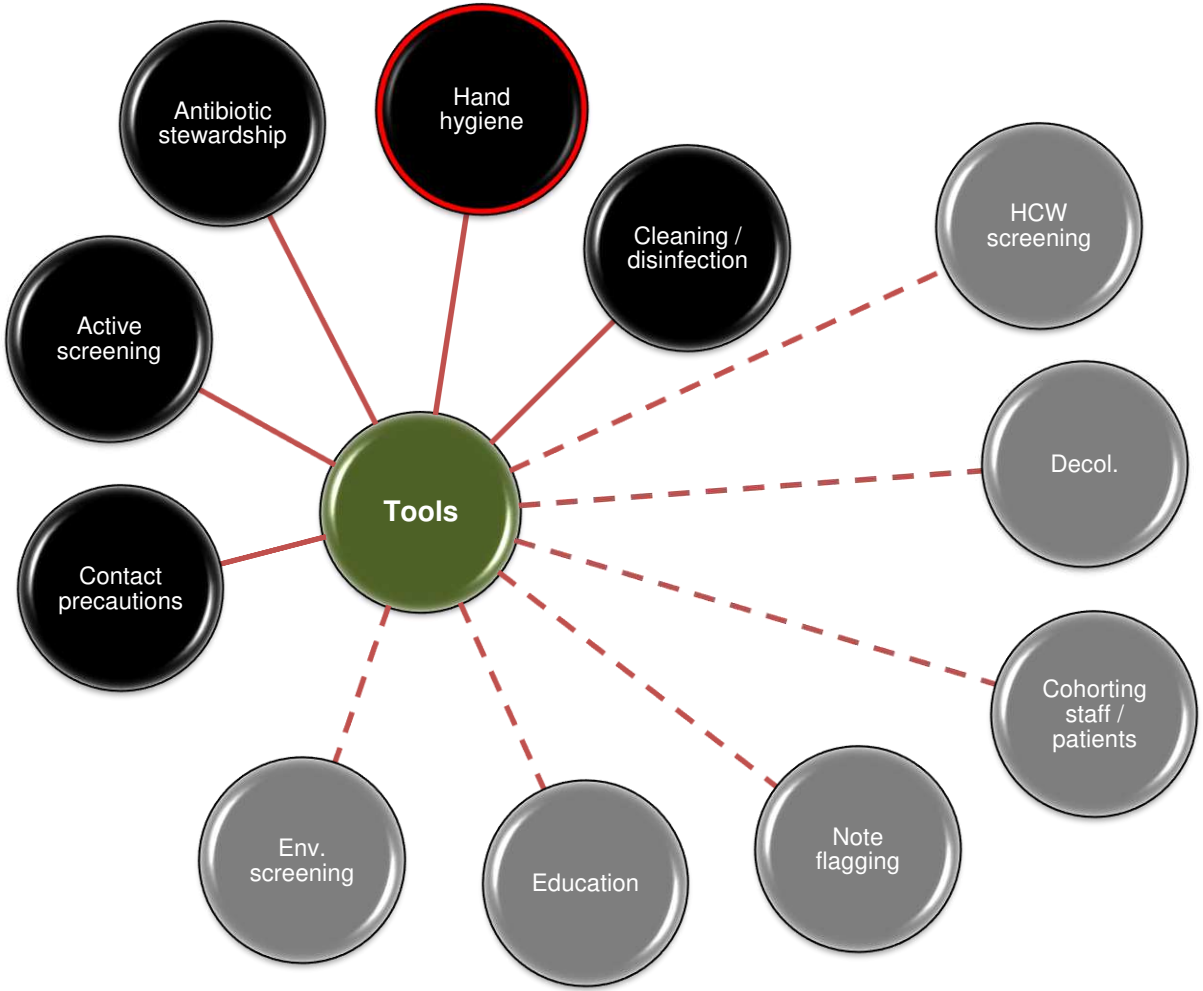
Colonisation often precedes infection for MDROs

Meta-analyses of subsequent infection in patients first identified as colonised with CPE/VRE.

	Any infection			Bloodstream infection		
	N studies	N infected / N colonised	Cumulative incidence (95% CI), %	N studies	N infected / N colonised	Cumulative incidence (95% CI), %
MDR-GNB	32	845/9034	0·14 (0·10–0·18)	23	434/8307	0·07 (0·04–0·11)
CRE or CPE	19	602/4547	0·19 (0·15–0·25)	14	347/4142	0·10 (0·07–0·15)
ESBL-E or 3GCR-E	14	235/4461	0·08 (0·05–0·13)	9	70/4087	0·04 (0·02–0·07)
E. coli	7	133/3098	0·08 (0·04–0·14)	6	46/3042	0·04 (0·01–0·10)
K. pneumoniae	4	59/741	0·09 (0·06–0·13)	3	14/730	0·02 (0·01–0·05)
VRE	16	329/5015	0·07 (0·04–0·12)	10	163/1840	0·10 (0·06–0·16)

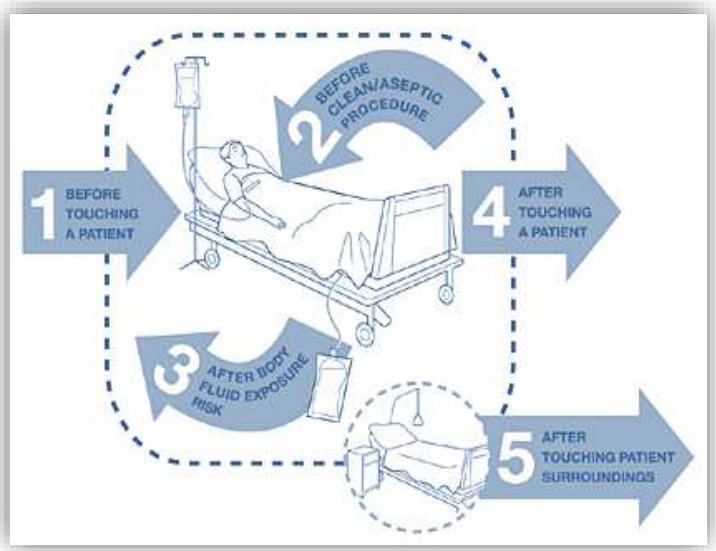
Incidence for CP-CRE was 26% (95% CI 19–35)

Willems et al. Lancet Infect Dis 2023.



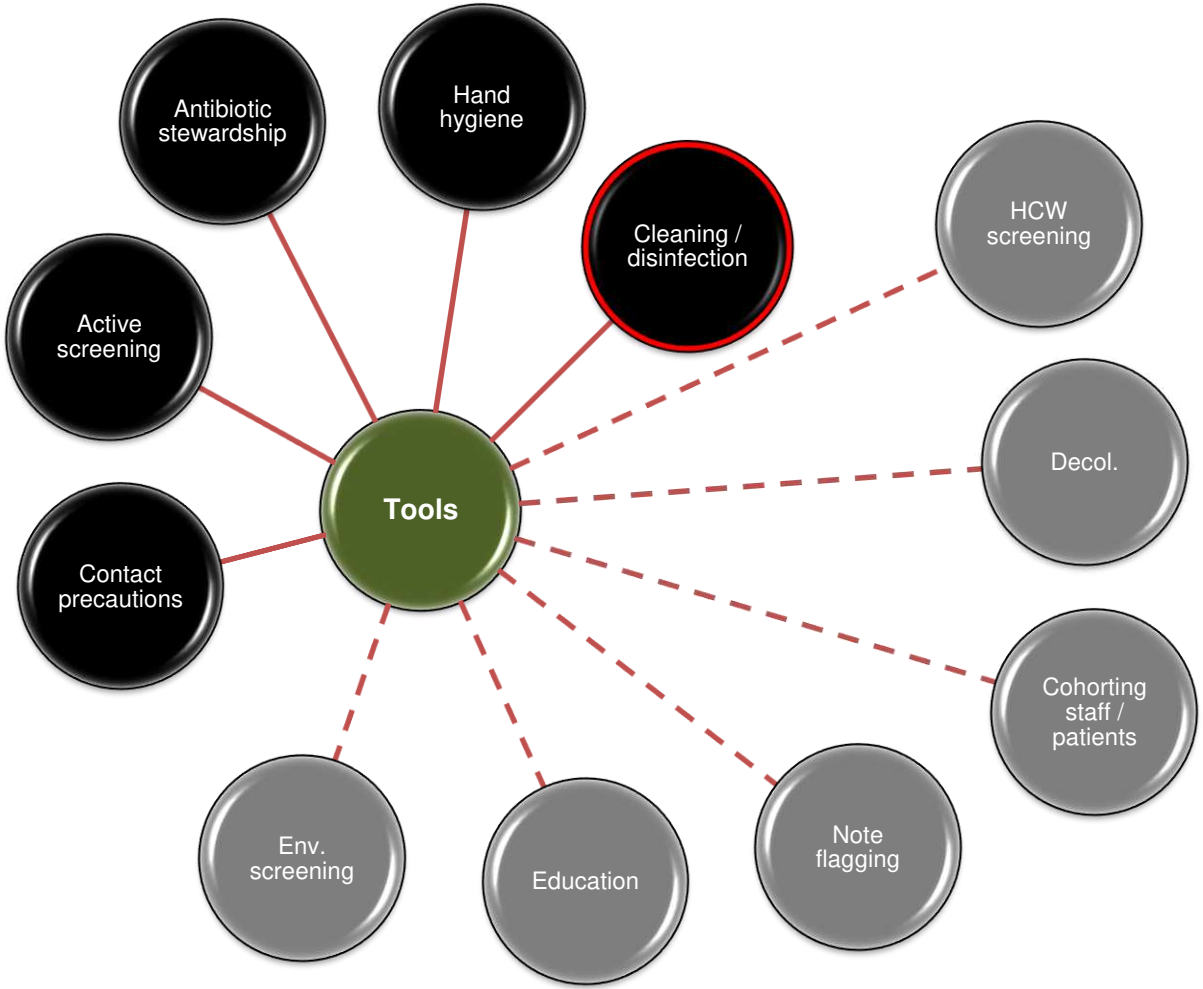
Otter *et al. Clin Microbiol Infect* 2015 2015;21:1057–1066.

Contaminated hands

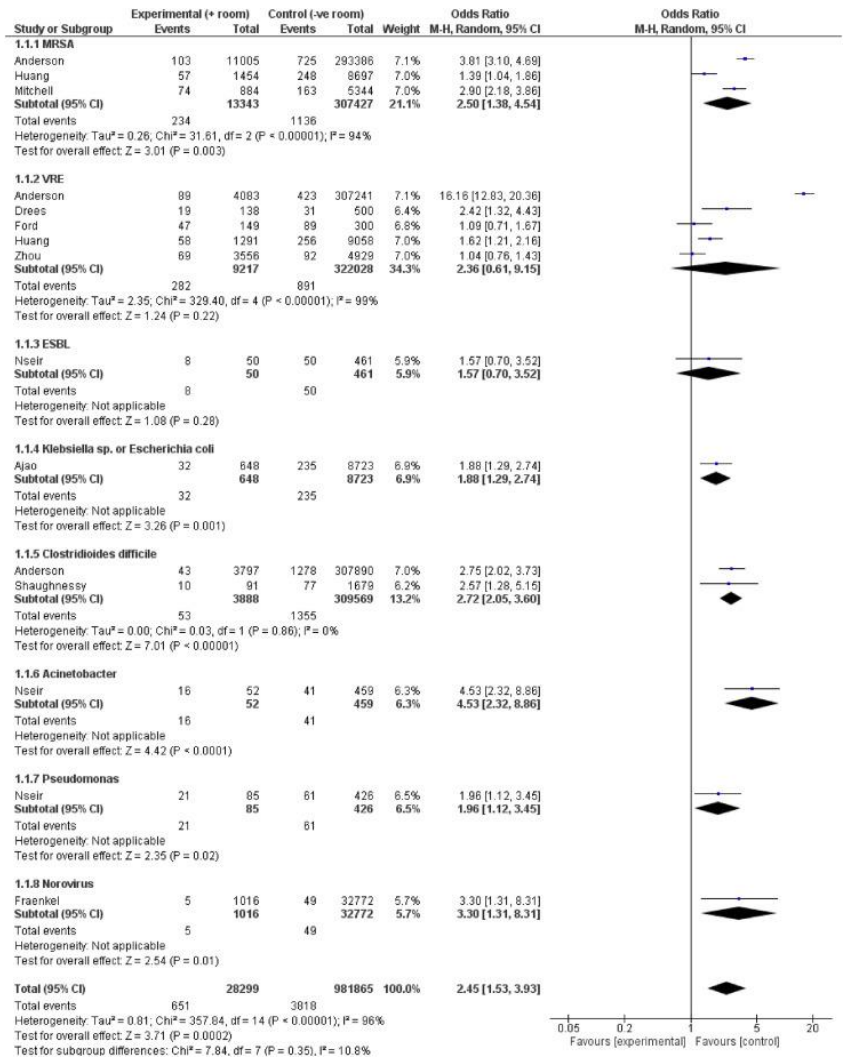


40%

Erasmus *et al. Infect Control Hosp Epidemiol* 2010;31:283-94.



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



The MDRO status of the prior room occupant influences acquisition risk

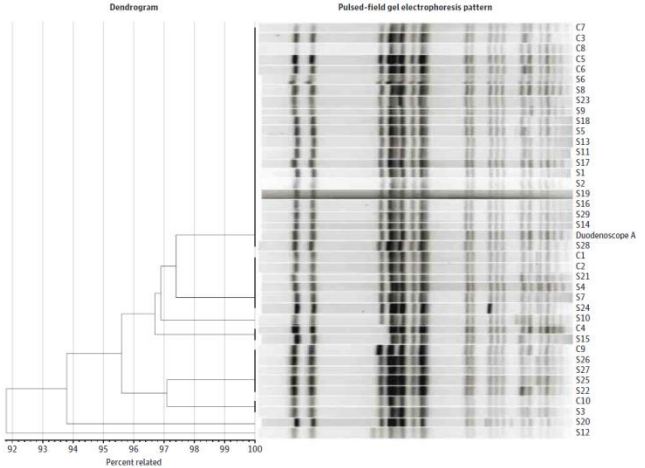
Meta-analysis of studies evaluating the risk of MDRO acquisition for the incoming occupant based on the status of the prior room occupant.

	OR	95% CI
Acinetobacter	4.5	2.3-8.9
Norovirus	3.3	1.3-8.3
C. difficile	2.7	2.0-3.6
MRSA	2.5	1.4-4.5
VRE	2.4	0.6-9.1
Pseudomonas	2.0	1.1-3.4
Klebsiella or *E. coli*	1.9	1.3-2.7
ESBL	1.6	0.7-3.5
Total	2.5	1.5-3.9

Mitchell et al. Infect Dis Health 2023.

When medical device decon fails…

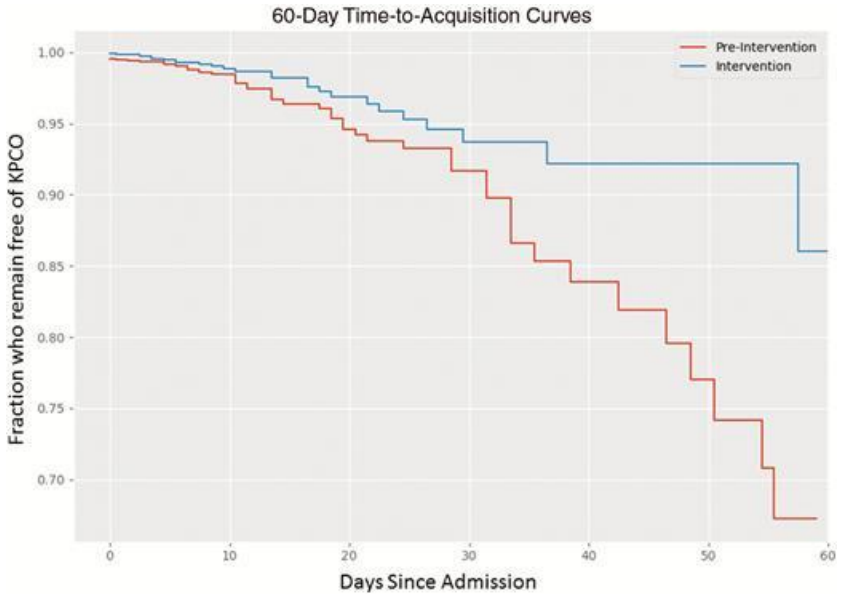
- 39 patient CRE outbreak in 2013 in Illinois.[1]
- Odds ratio for duodenoscope exposure in case patients 78 (95% CI 6-1008).
- No breakdown in compliance with decon procedures; has prompted a global review and change in the way that these devices are decontaminated.[2]
- *Meticulously cleaning duodenoscopes prior to high-level disinfection should reduce the risk of transmitting infection, but may not entirely eliminate it. (FDA Feb 23 2015).*



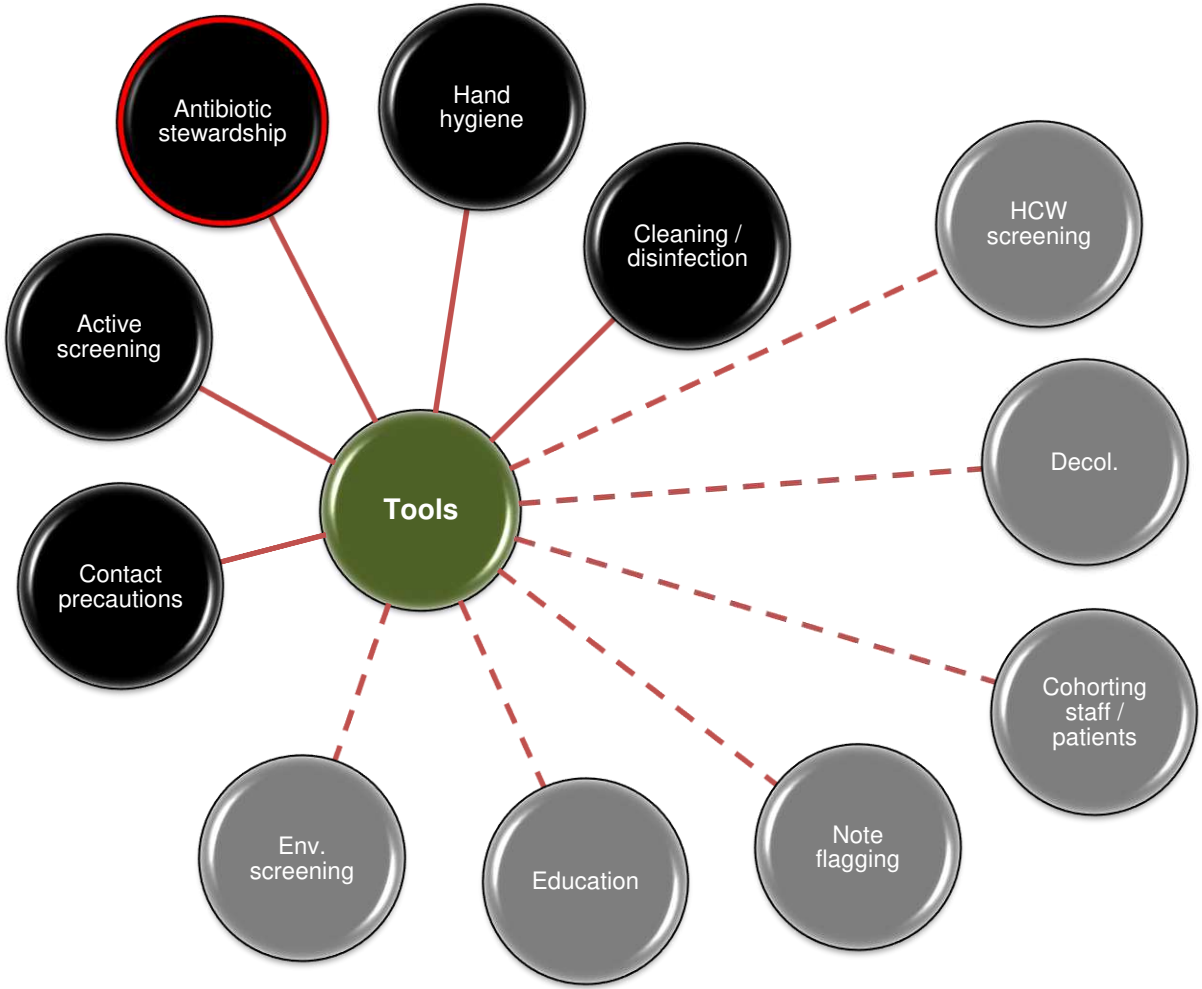
1. Epstein *et al. JAMA*. 2014;312:1447-55.
2. Rutala & Weber. *Am J Infect Control* 2016;44 (Suppl):e47-51

Contaminated sinks / drains

- CPE (*K. pneumoniae*) acquisition and clinical infection halved through improved management of sinks (OR = 0.51 for acquisions, and 0.29 for clinical cultures) (n=~7,500 pts).

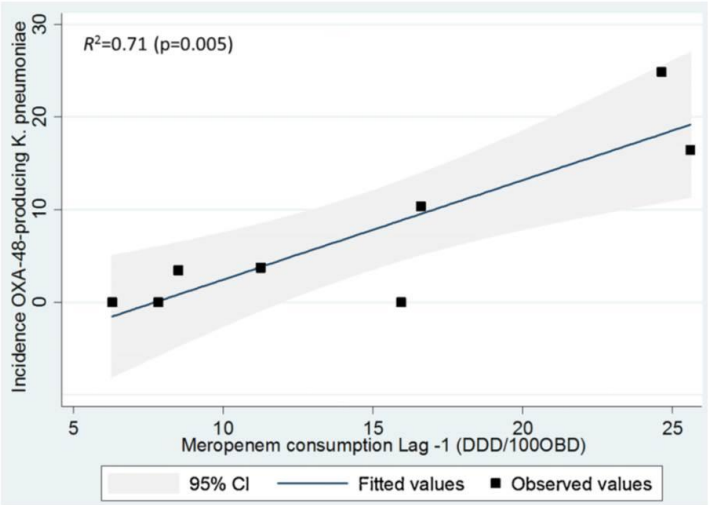


Mathers *et al. Clin Infect Dis* 2018 in press.



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

Can we forecast a CPE storm?



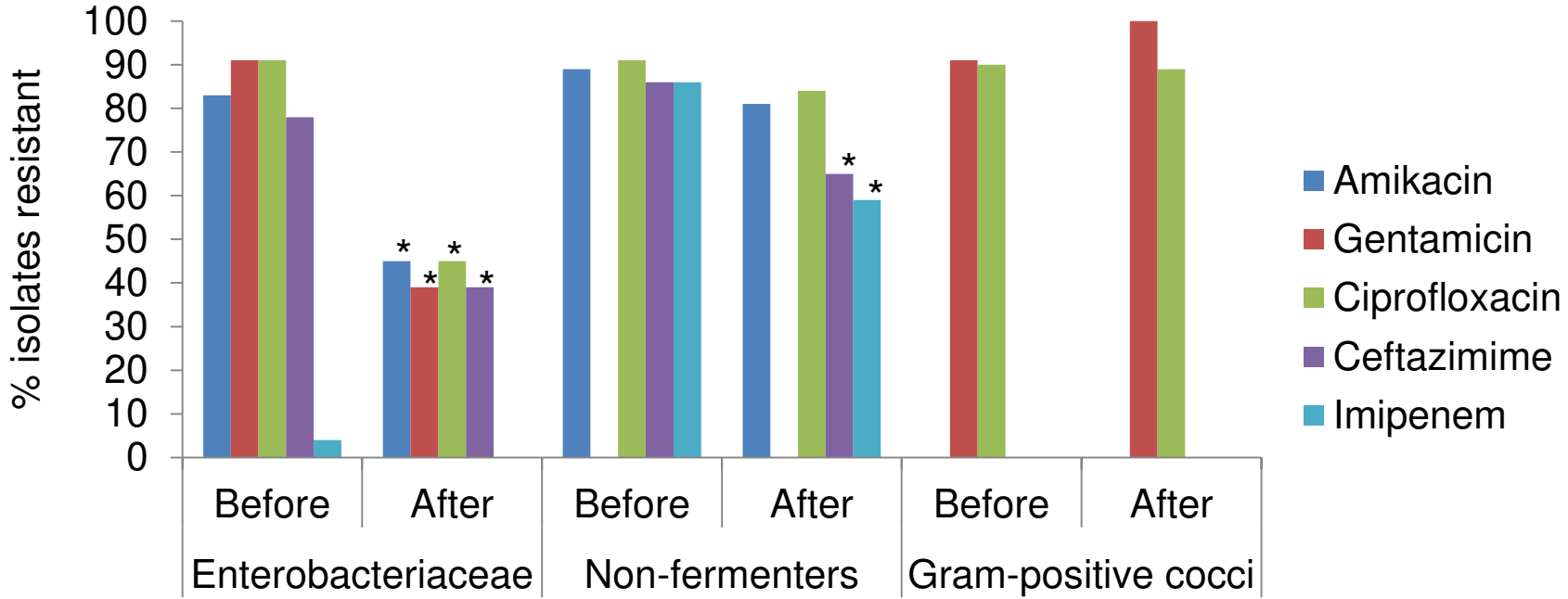
What drives carbapenem resistance? The use of meropenem in the previous year plotted against the incidence rate of OXA-48-producing K. pneumoniae

- Could we find and implement an “alert” level of carbapenem use?
- The paper reports that 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 Enterobacterales and non-fermenters?

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

Antibiotic use

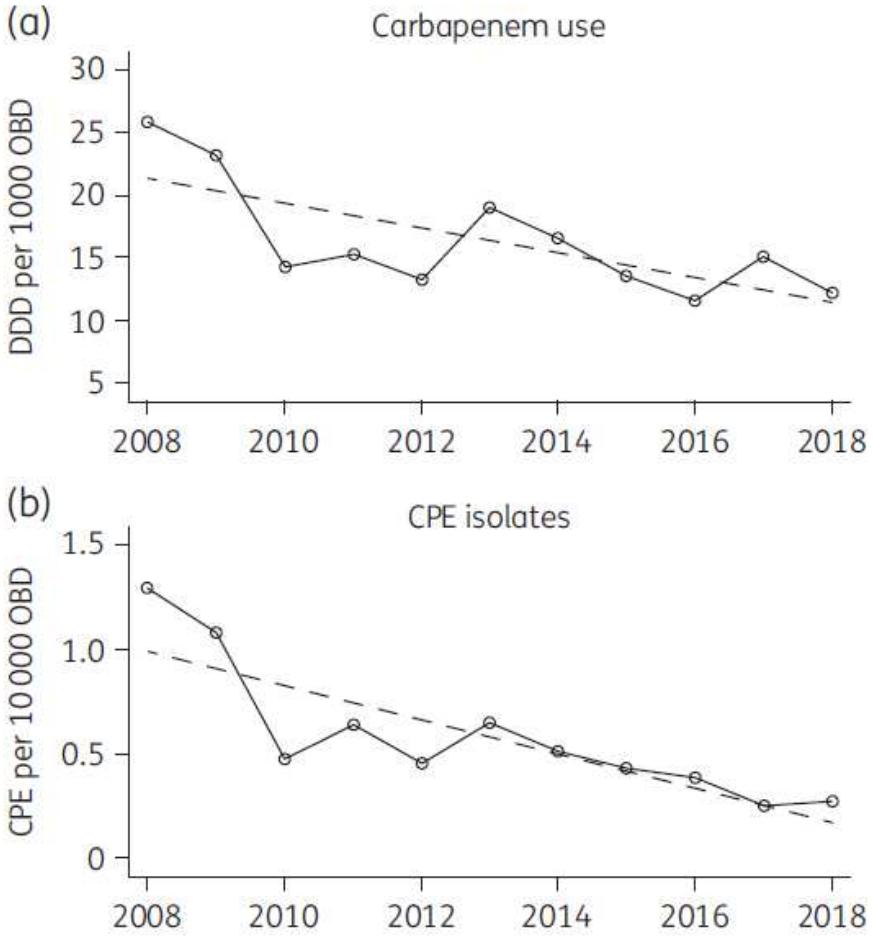
Evaluating impact of 6 month antimicrobial stewardship intervention on an ICU by comparing bacterial resistance for matched 6 month periods either side of intervention.



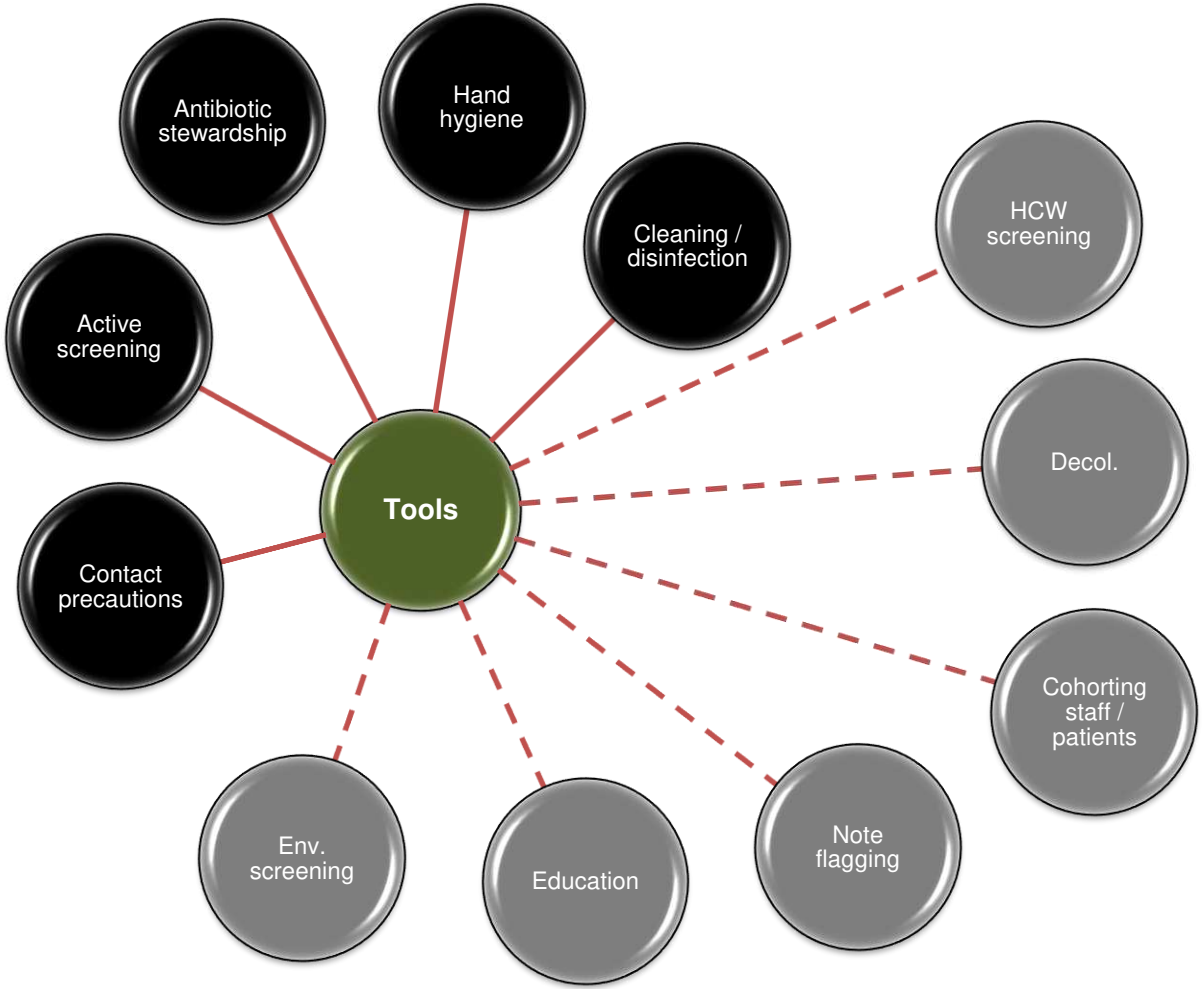
Hou *et al. PLoS ONE* 2014;9:e101447; * = significant difference before vs. after.

Antibiotic use

Impact of an antimicrobial stewardship programme on carbapenem consumption and CPE in an Australian local health district.



Cipko et al. J Antimicrob Chemother AMR 2020.



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

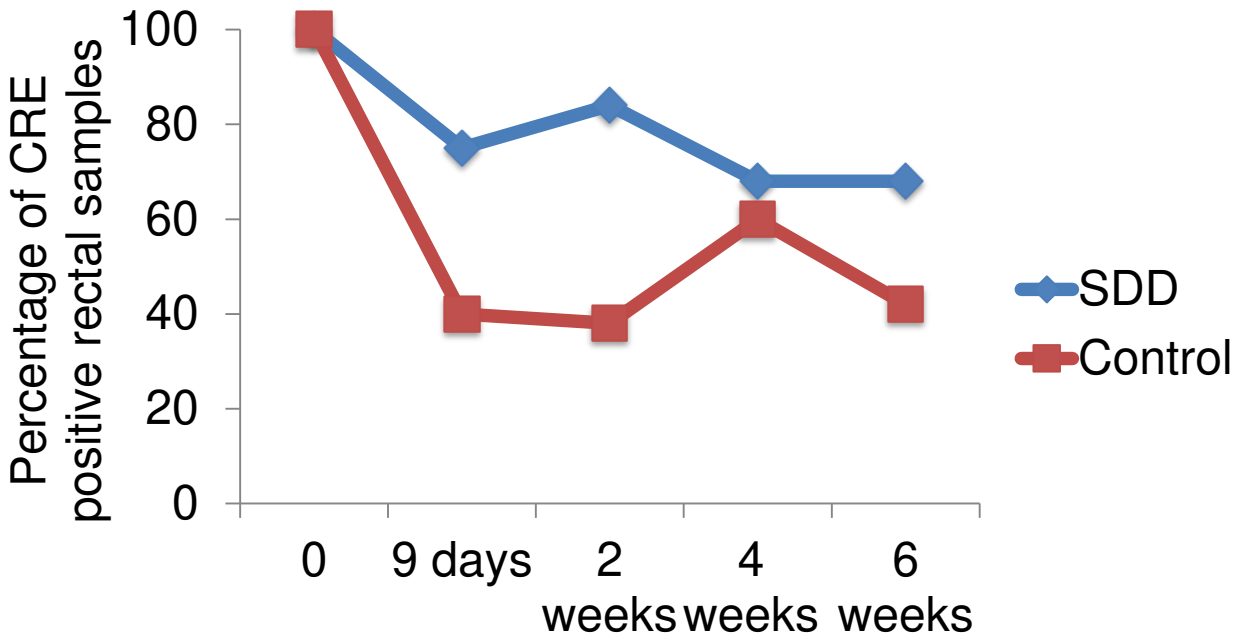
Deisolation?

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

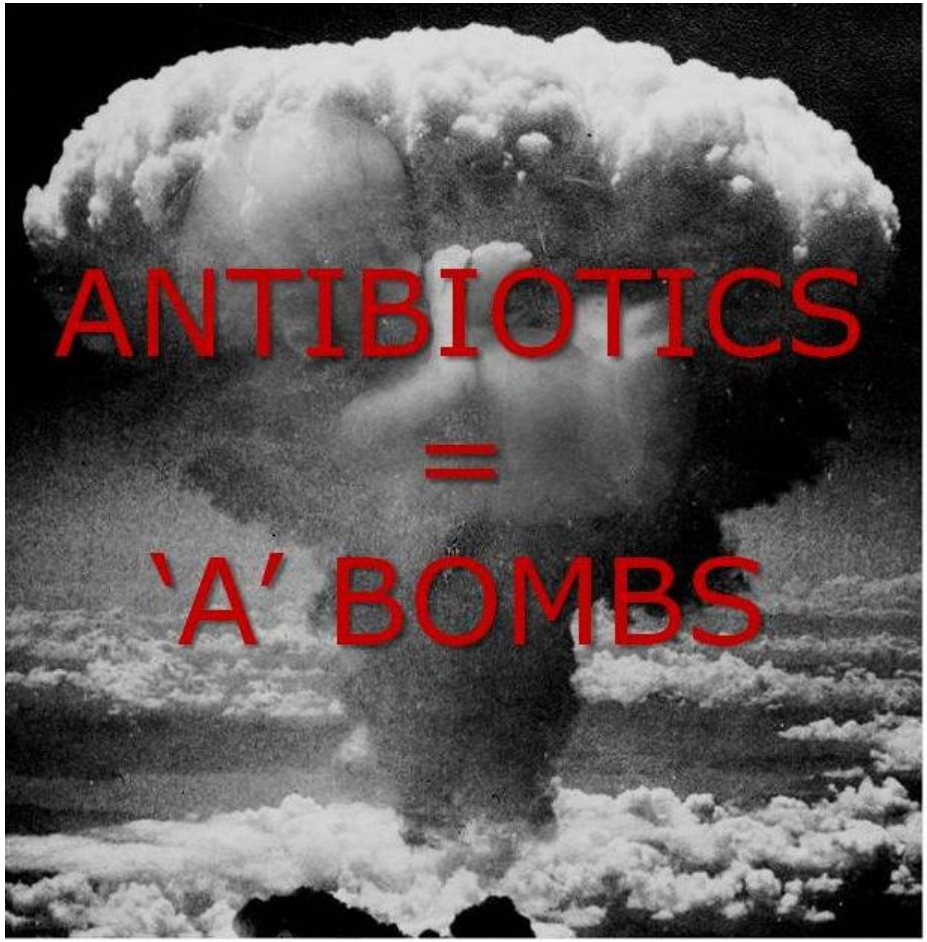
1. Bird *et al. J Hosp Infect* 1998;40:243-247.
2. Pacio *et al. Infect Control Hosp Epidemiol* 2003;24:246-250.
3. Zahar *et al. J Hosp Infect* 2010;75:76-78.
4. O'Fallon *et al. Clin Infect Dis* 2009;48:1375-1381.
5. Zimmerman *et al. Am J Infect Control* 2013;41:190-194.

‘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.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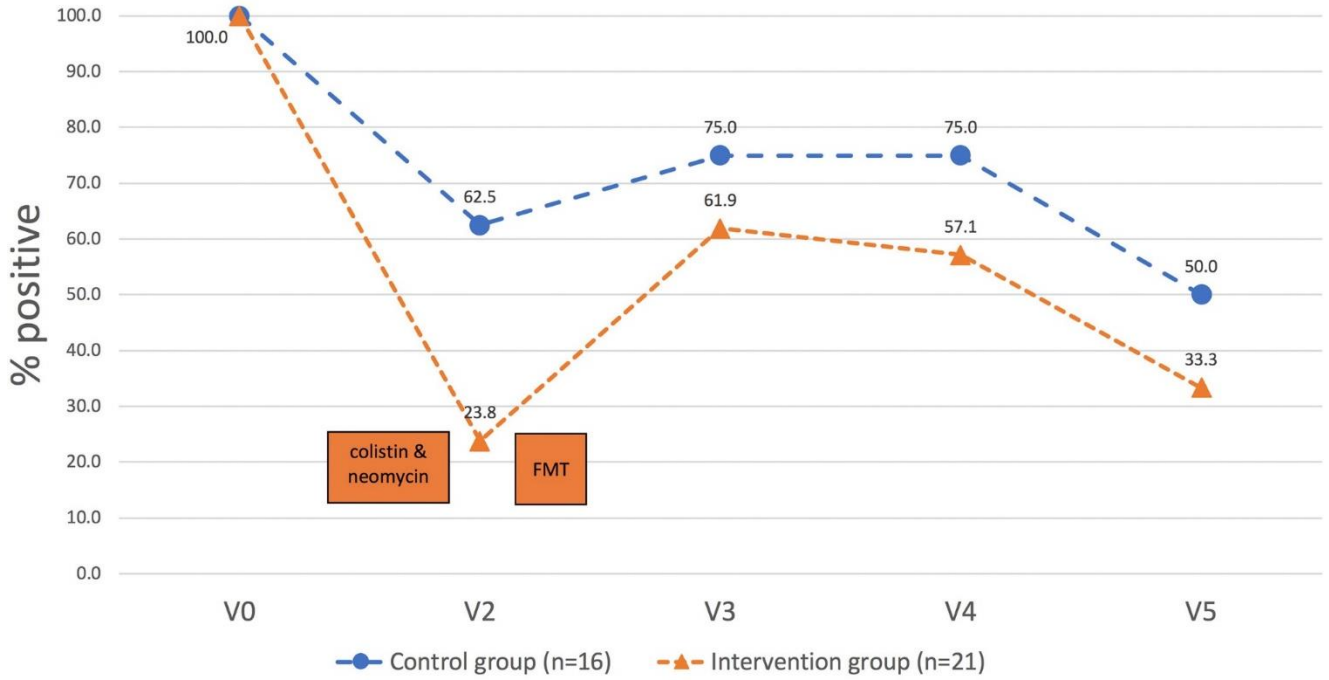
Decolonisation using FMT

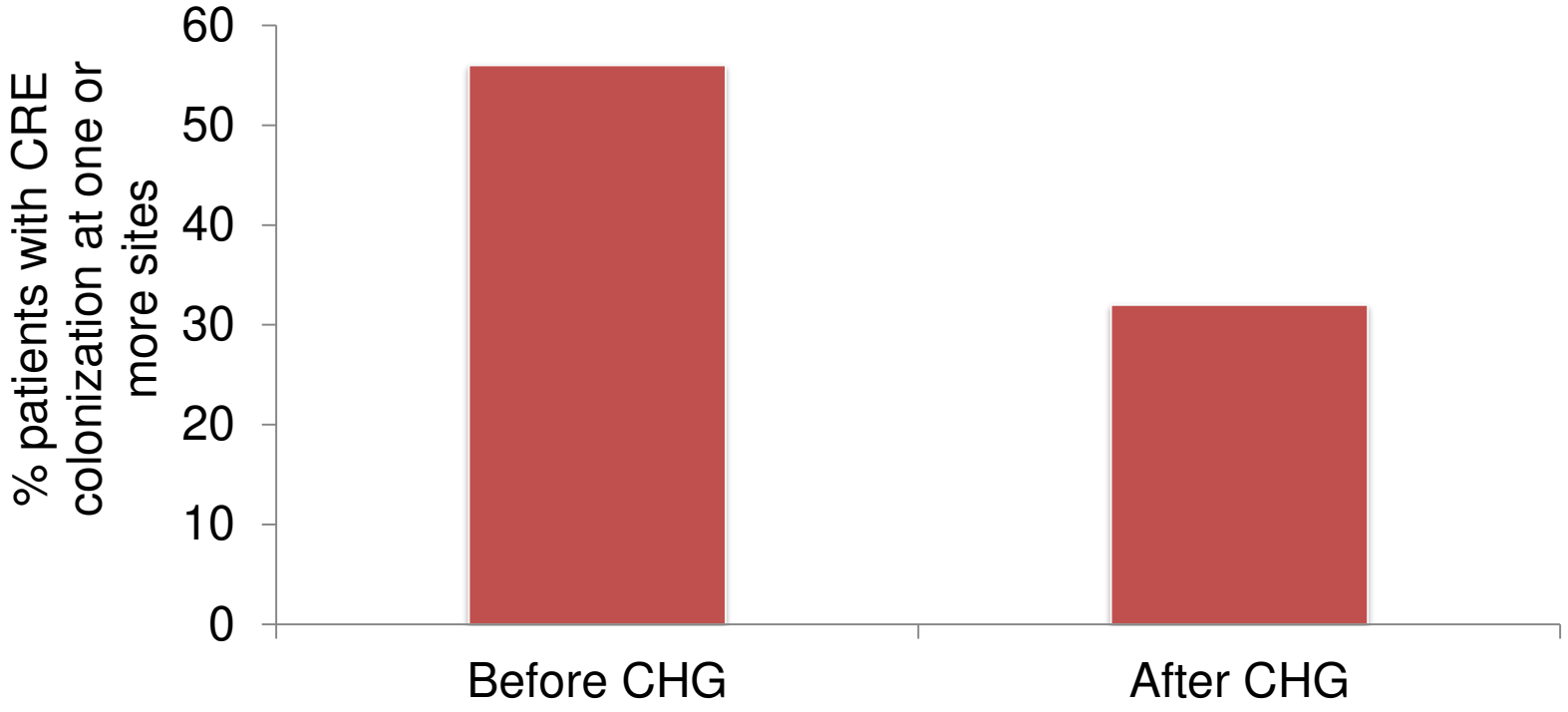
39 ESBL or CPE colonized patients randomised to oral abx + FMT (brown(!) line) or no intervention (blue line)



Huttner et al. Clin Microbiol Infect 2019.

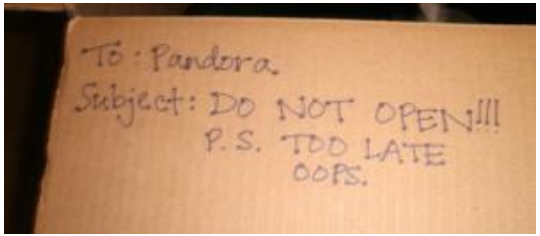
Chlorhexidine – efficacy

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.

Colonised staff?



Multidrug-resistant organism growth from perirectal swabs

Culture result	Healthcare personnel participants[a] ($n = 379$) n (%)	Control participants[a] ($n = 376$) n (%)	p value
No MDRO growth	364 (96.0)	364 (96.8)	0.55
Vancomycin-resistant enterococci (VRE)	0	0	—
ESBL-producing organisms	15 (4.0)	11 (2.9)	0.55
Carbapenemase-producing organisms	0	1 (0.3)	0.50

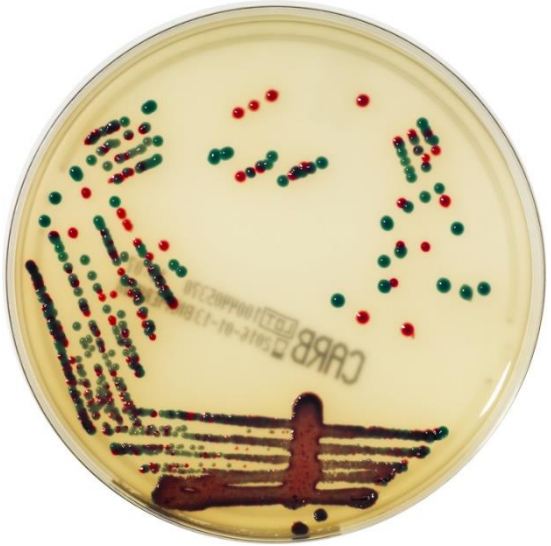
Abbreviation: ESBL, extended spectrum β-lactamase; MDRO, multidrug-resistant organism.
[a] Includes participants who did not submit questionnaires.

Decker *et al. Clin Microbiol Infect* 2018;24:82.e1-82.e4.

Which is the most important intervention to prevention the spread of CPE?

- Screening & isolation
- Hand hygiene
- Cleaning / disinfection
- Antibiotic stewardship

The rising threat from carbapenem-resistant organisms, and how to control them



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