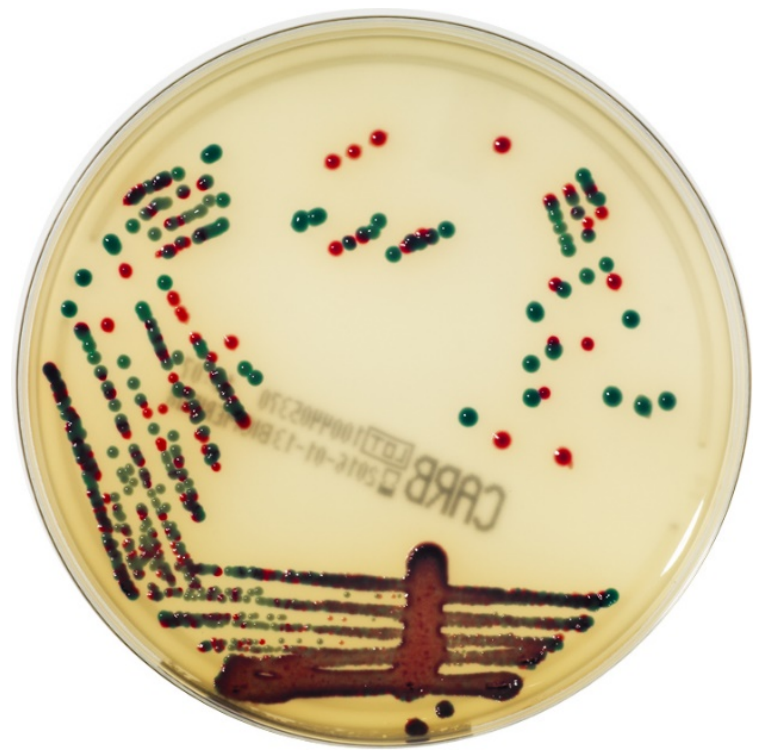


# Carbapenem-resistant Enterobacterales in healthcare and community settings



Jon Otter PhD FRCPATH,  
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Guy's and St Thomas' NHS Foundation Trust  
Honorary Senior Lecture in HCAI & AMR, Imperial College London

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**Imperial College  
London**



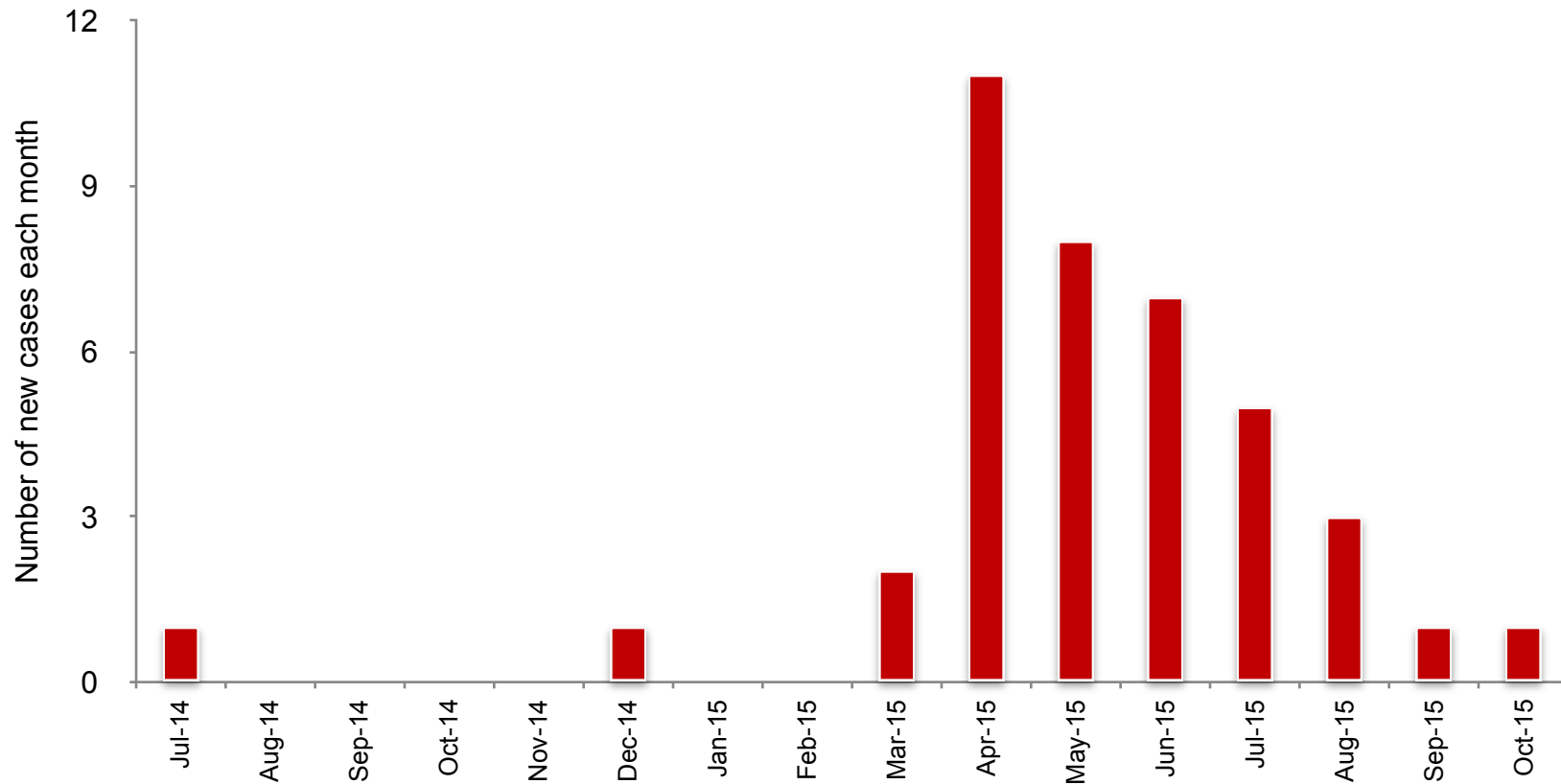
**Guy's and St Thomas'  
NHS Foundation Trust**



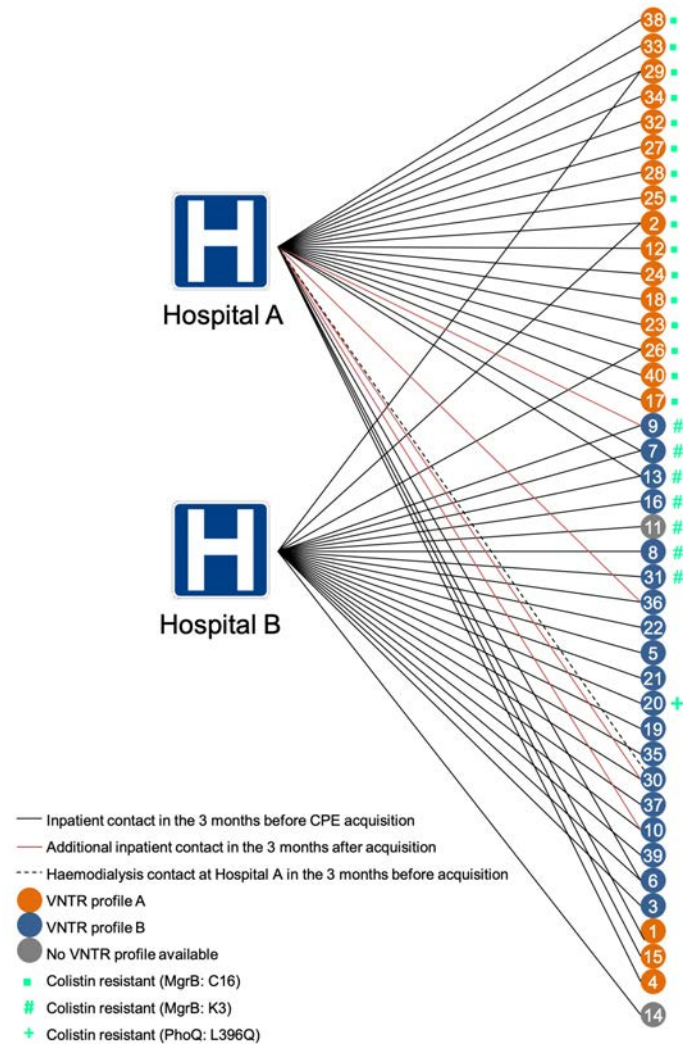
What's the problem?

# 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

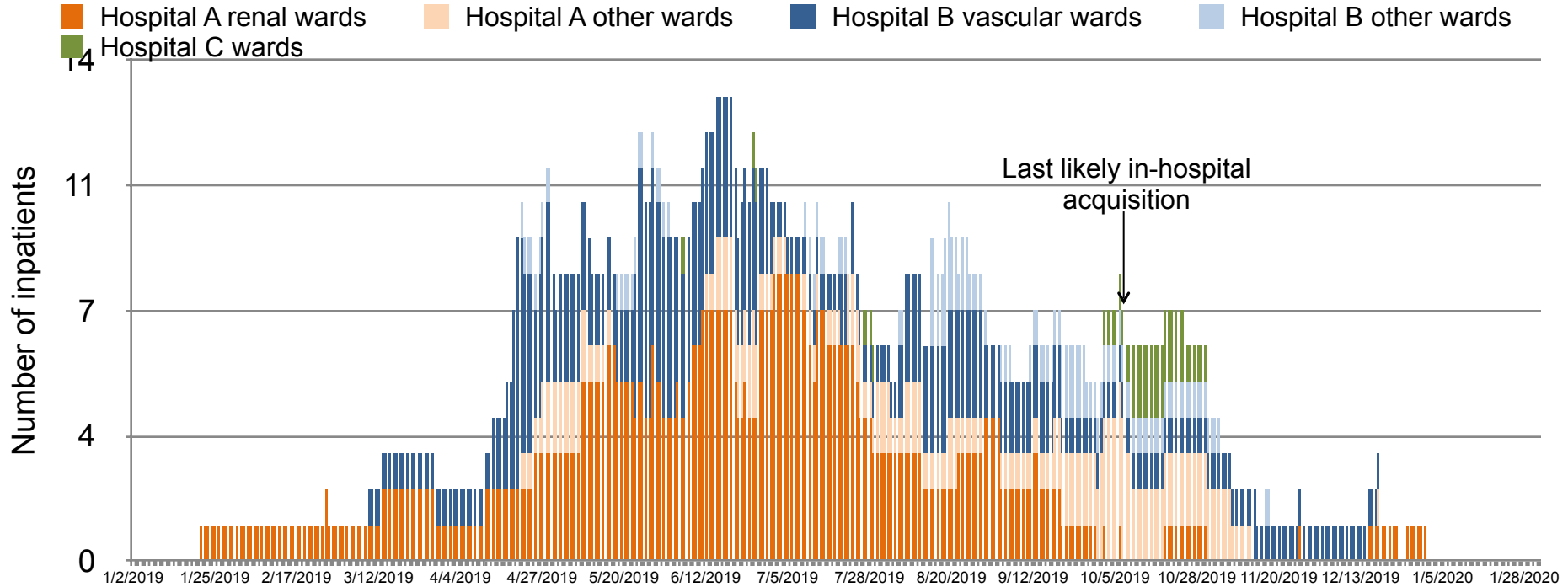


# Emergence of colistin resistance

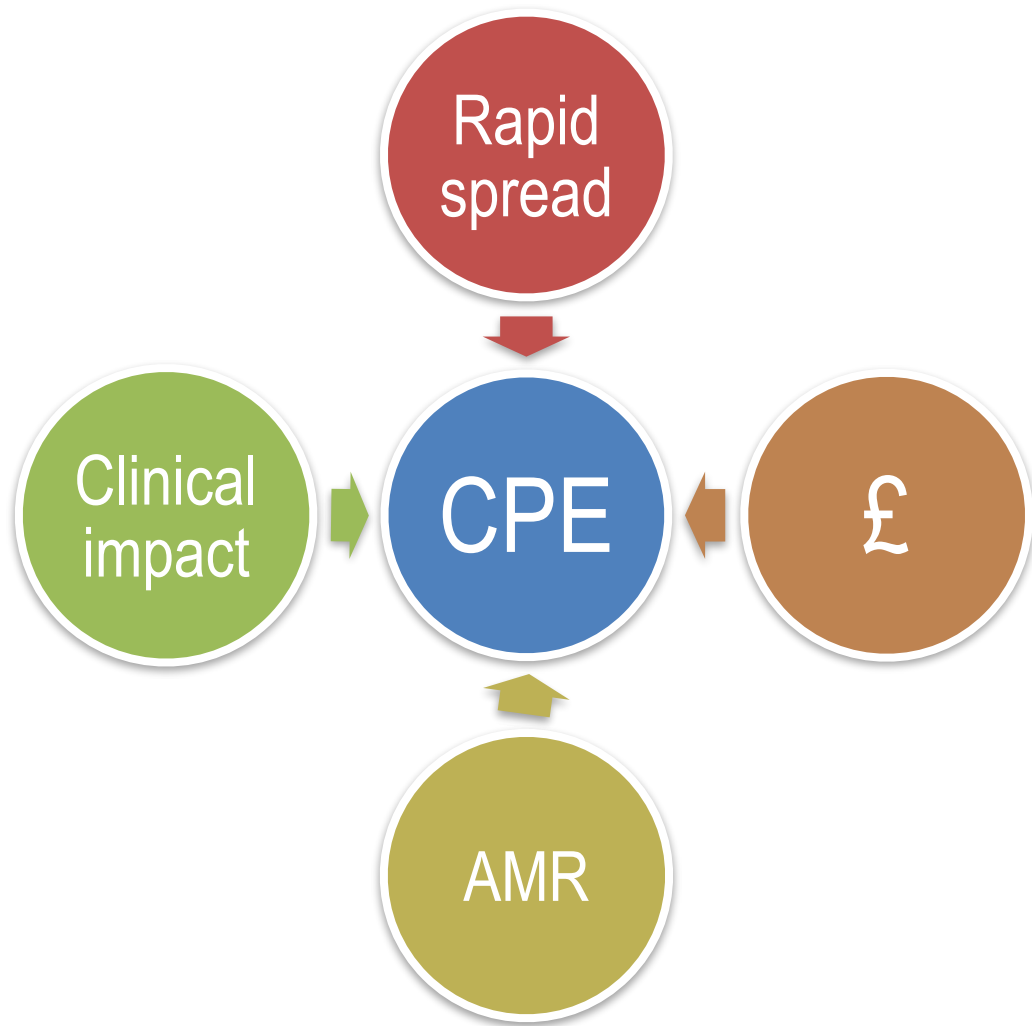


# Contact precautions

The number of inpatients with known CPE carriage, daily

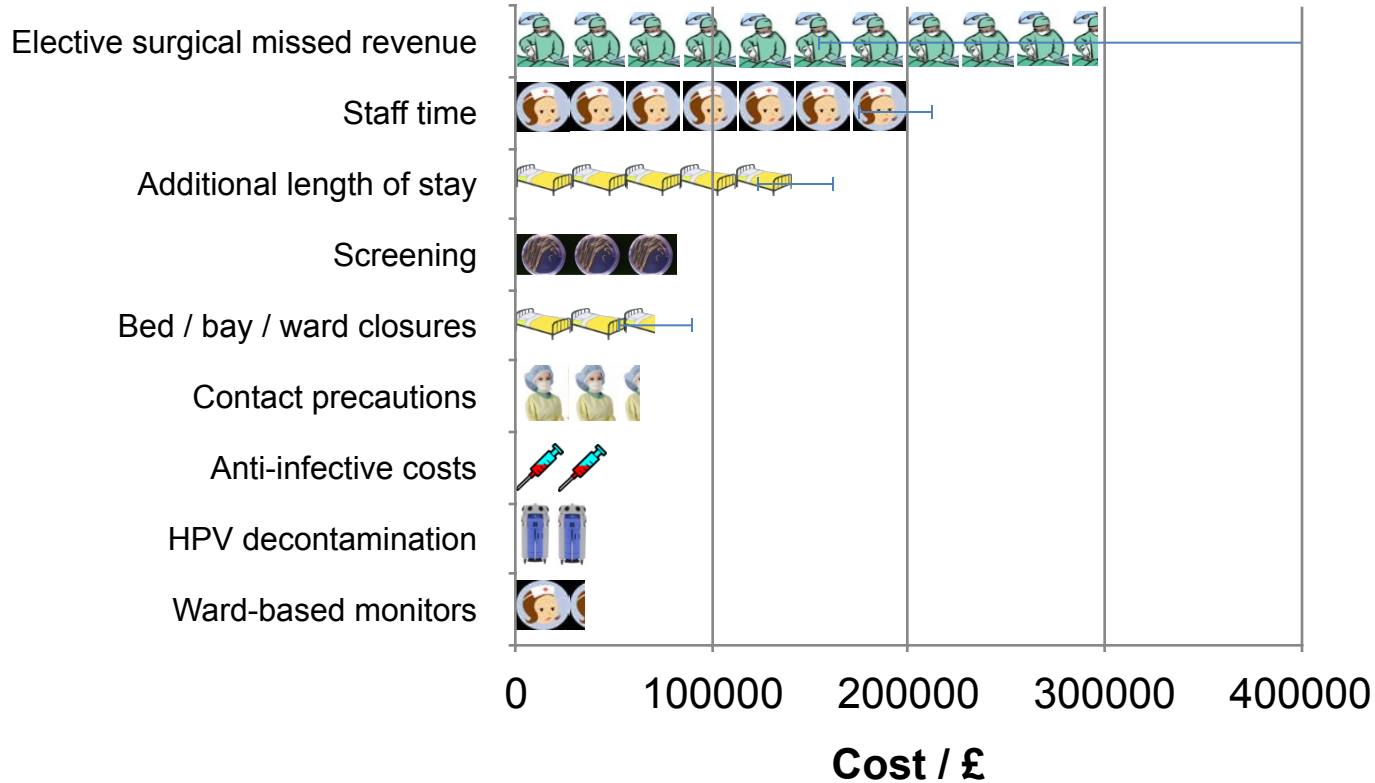


1831 contact precautions days generated, at a cost of £61,575 (£37,389 in gloves and aprons, £23,588 in stock disposal, and £598 in infectious waste disposal)



# What's the problem? ££££

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

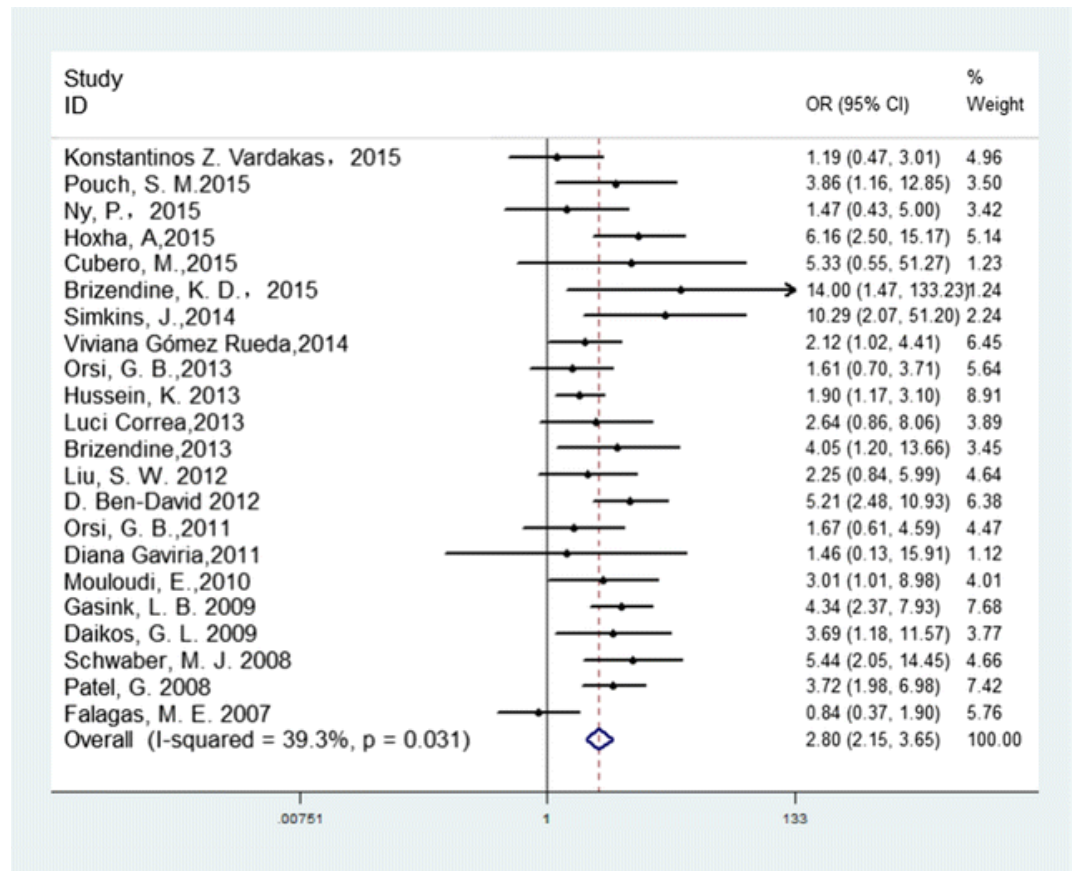


# What's the problem? Resistance

	30 Jun 2014 00:00	BC - Blood culture	AICU - AICU	CNS - Coagulase Negative Staphylococcus GPC - Unidentified Gram positive coccus SE - Staphylococcus epidermidis	
	30 Jun 2014 00:00	ASC - Ascitic fluid	AICU - AICU	KP - Klebsiella pneumoniae	
<b>Organism</b> 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

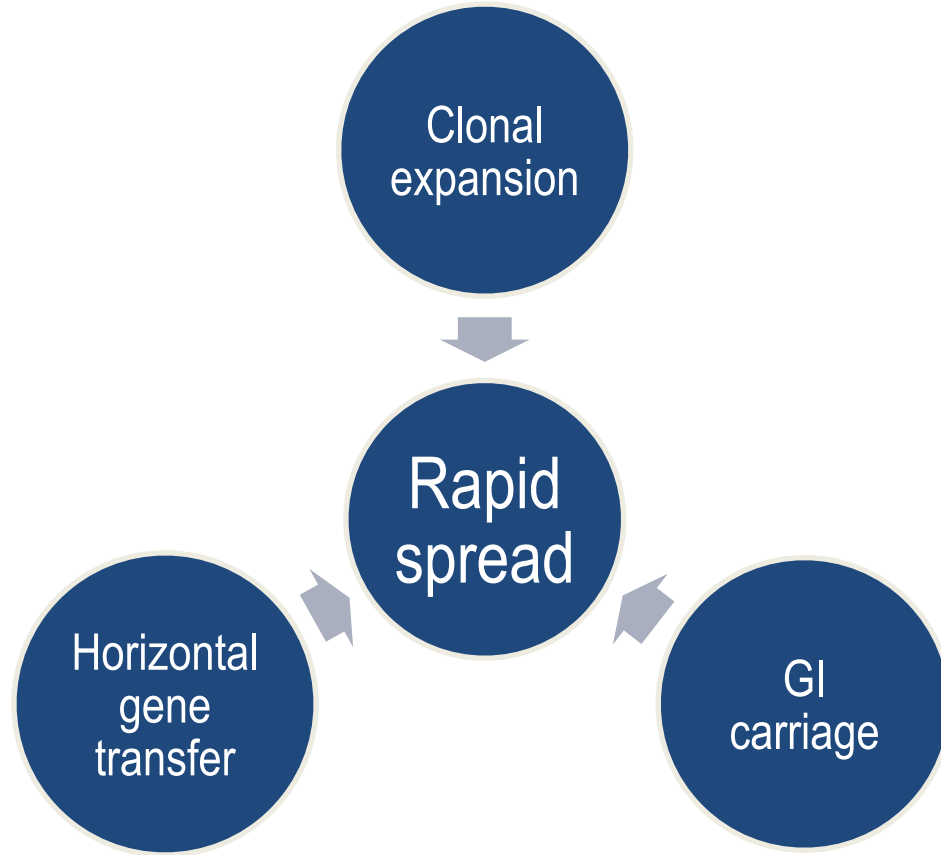
# Carbapenem-resistant bloodstream infection is really bad news in ICU – and not all CPE are equal

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.

<b>Carbapenam-resistant Gram negative bacilli</b>	<b>Crude 30-Day Mortality</b>	<b>Adjusted Odds Ratio of Death</b>	<b>Attributable Mortality, Controls: Patients With Carbapenam-Susceptible Bloodstream Infection</b>
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 <i>Pseudomonas aeruginosa</i>	32.8%	2.99 (1.48–5.95)	19%
CR <i>Acinetobacter baumannii</i>	43.2%	2.65 (1.52–4.61)	16%

MBLs\* include NDM, VIM, and IMP carbapenemases

# What's the problem? Rapid spread



# Acronym minefield

CPE

MDR-GNR

CPC

ESBL

MDR-GNB

CRO

CPE

CRE

CRC

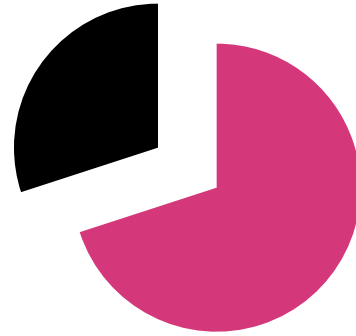
KPC

CRAB

# Rising threat from multidrug-resistant Gram-negative bacteria



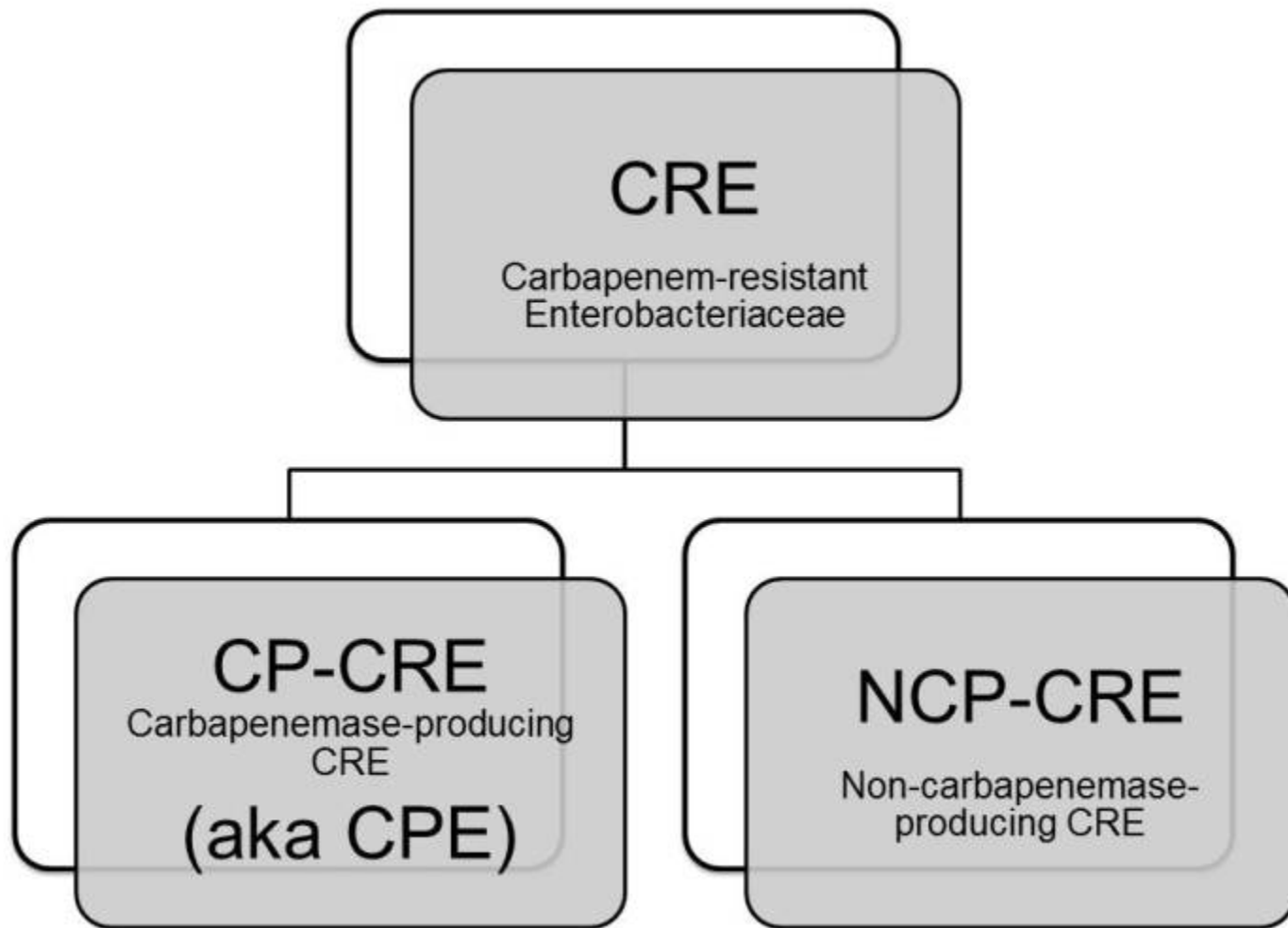
% of all HAI caused by GNRs.



% of ICU HAI caused by GNRs.

Non-fermenters	<i>Acinetobacter baumannii</i> <i>Pseudomonas aeruginosa</i> <i>Stenotrophomonas maltophilia</i>	<b>CPE</b>
Enterbacterales	<i>Klebsiella pneumoniae</i> <i>Escherichia coli</i> <i>Enterobacter cloacae</i>	

**CPO**

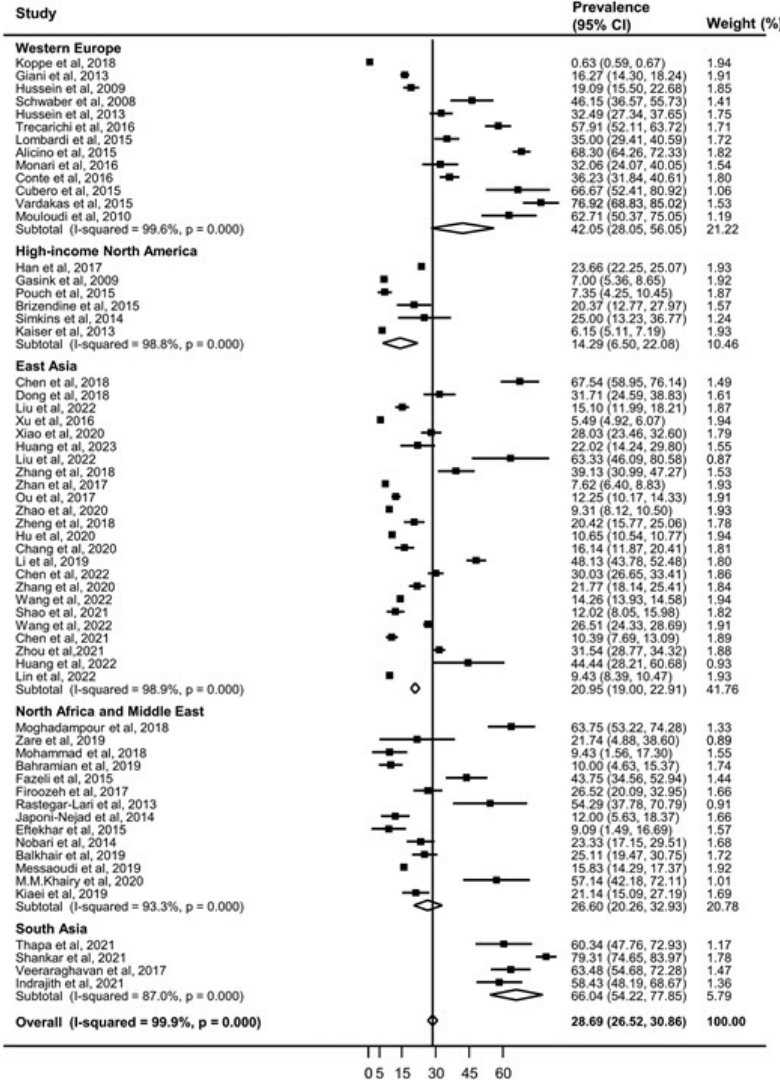
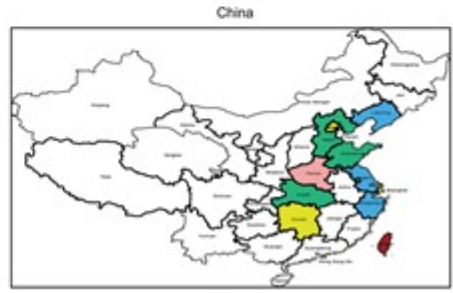
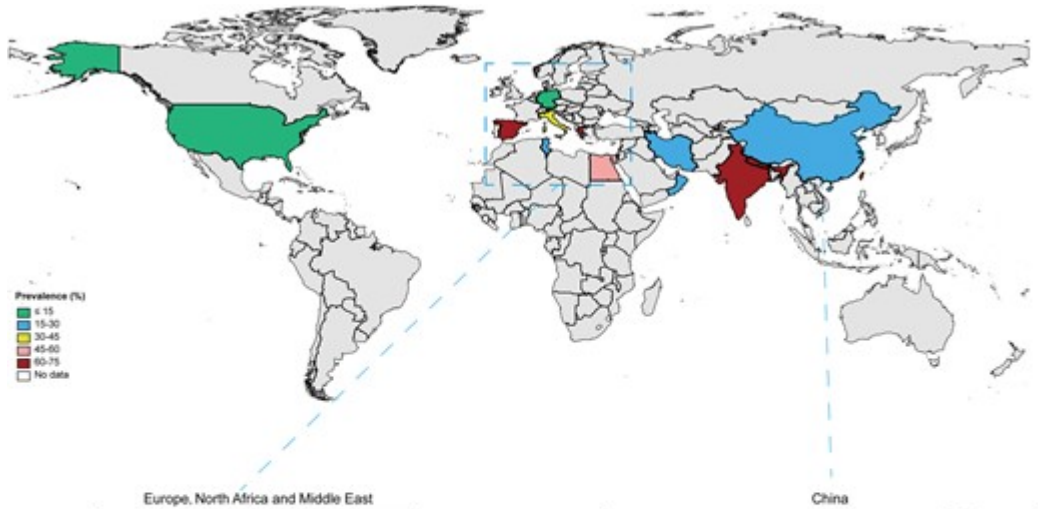


# The emerging threat of CPE

<b>Pathogen</b>	<b>CPE</b>	<b>MRSA</b>	<b>VRE</b>	<b><i>C. difficile</i></b>
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	+/-	+	++	+++

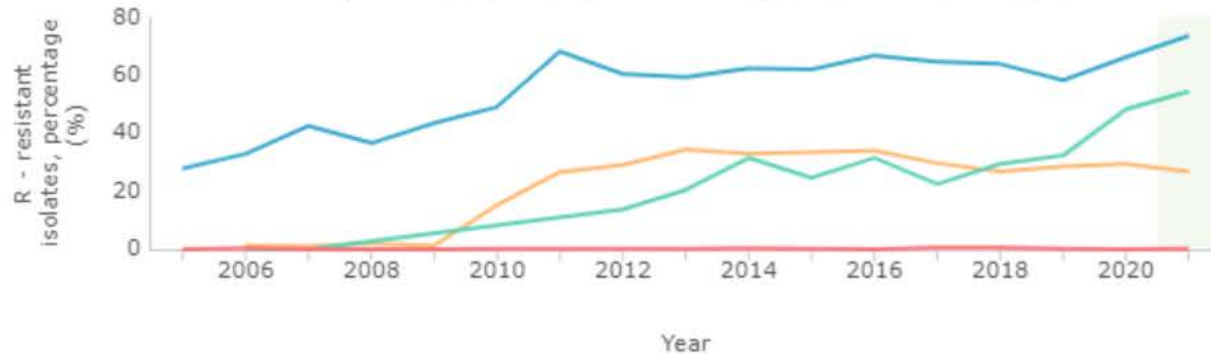
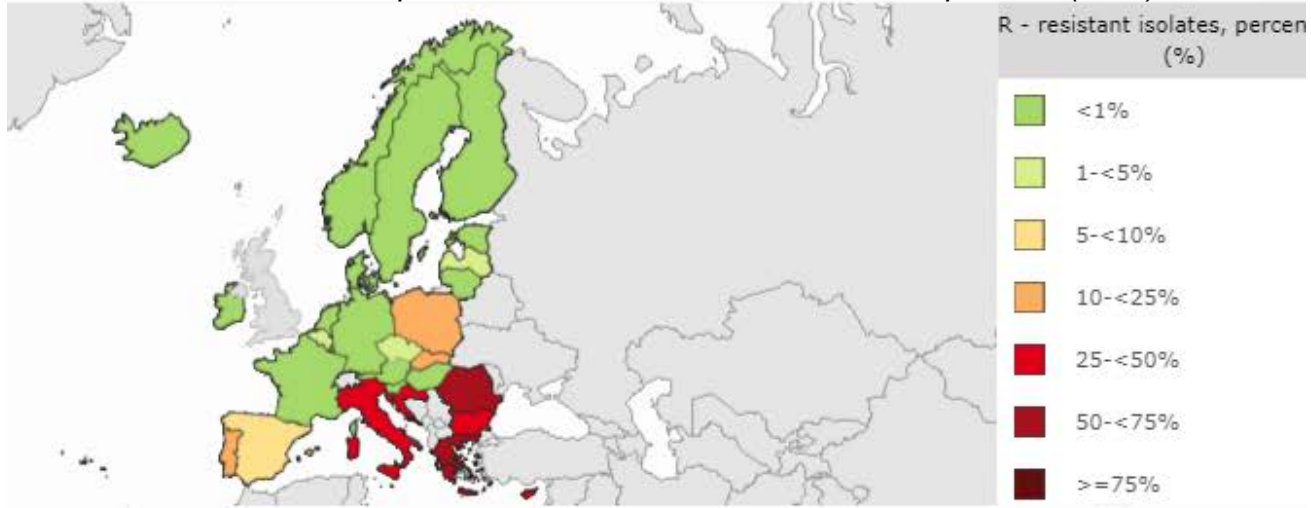
How bad is it?

# Global prevalence of CR amongst healthcare-associated *K. pneumoniae*



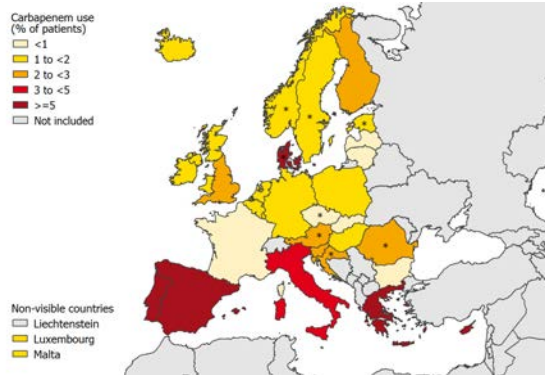
# CRE around Europe

% invasive *K. pneumoniae* isolates resistant to carbapenems (CRE)

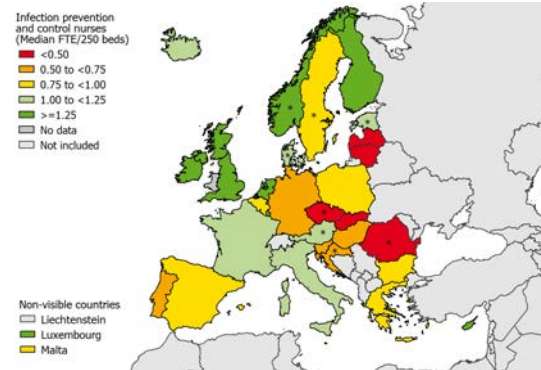


# What drives the European 'north-south divide'?

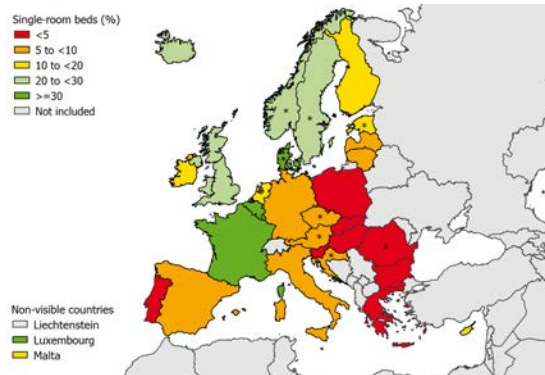
## Antibiotic use



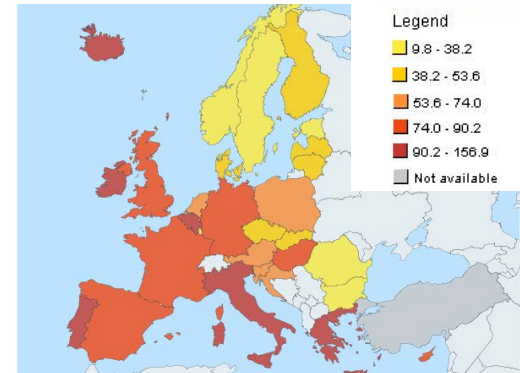
## Infection control staffing



## Single room availability



## National debt

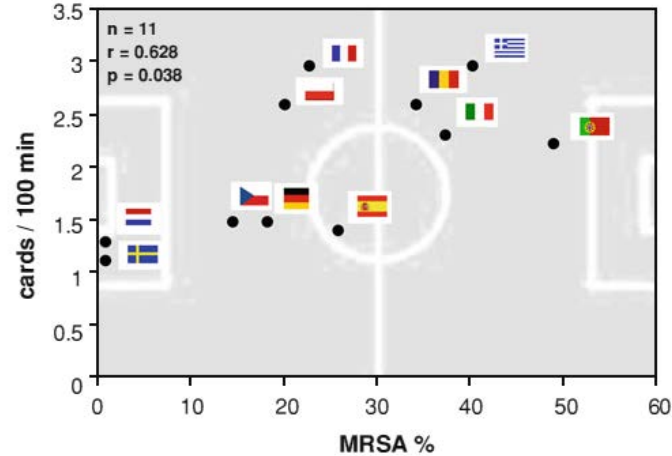


1. ECDC Point Prevalence Survey, 2013.

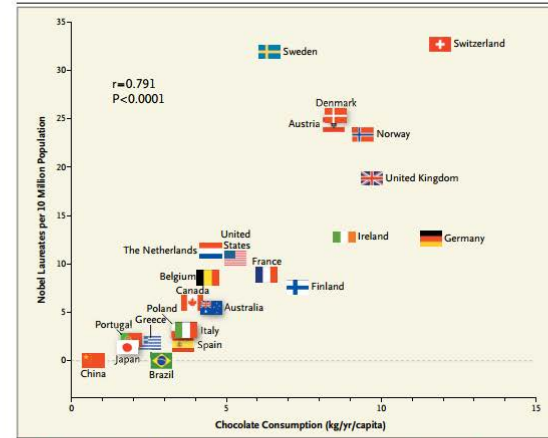
2. National debt as a percentage of GDP. ["Eurostat public debt GDP"](#) by Eurostat. Licensed under Attribution via Wikimedia Commons.

# 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)<sup>1</sup>



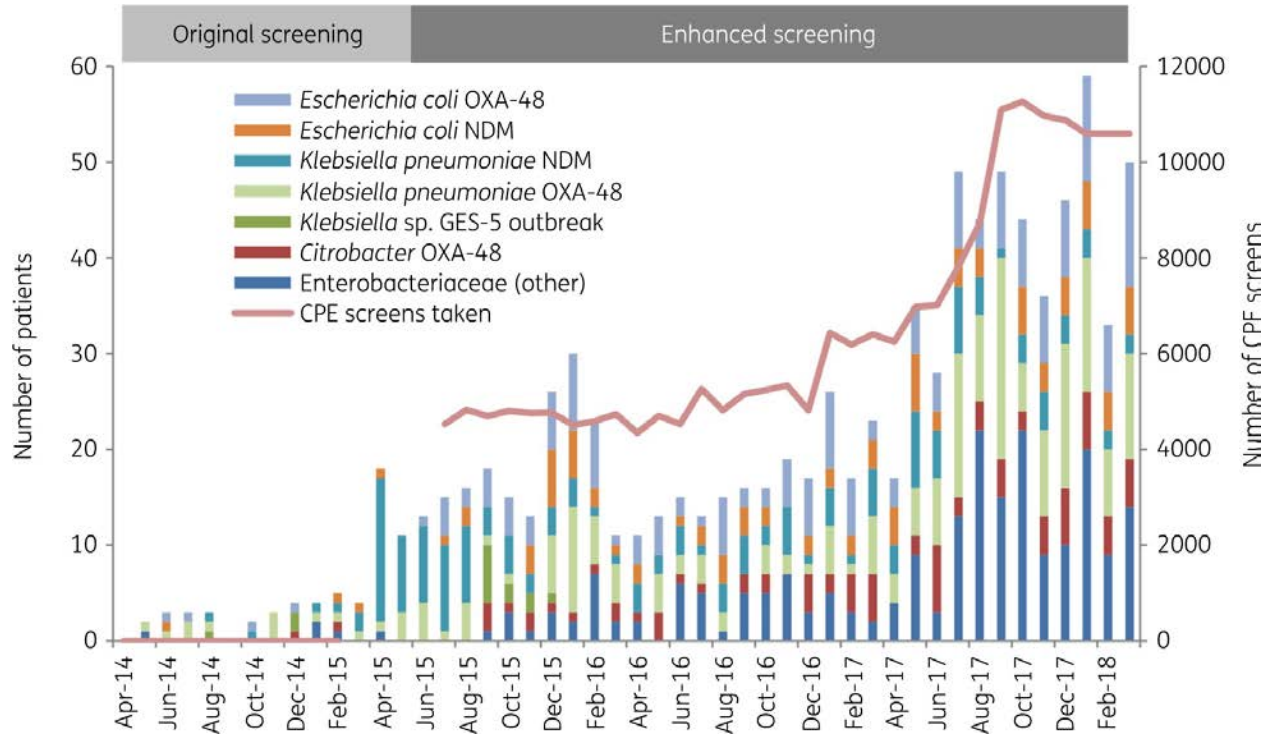
Correlation between national chocolate consumption and rate of Nobel prize winners.<sup>2</sup>



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





# Prevalence of carbapenem-resistant Enterobacterales in healthcare and community settings in the UK: a systematic review and meta-analysis

[H. Almadhoon](#)<sup>a</sup> · [I. Ahmad](#)<sup>b,†</sup> · [W.W.Y. Lee](#)<sup>c,†</sup> · ... · [D.M. Lecky](#)<sup>e</sup> · [A.H. Holmes](#)<sup>a,c,f,g</sup> · [N.J. Zhu](#)<sup>a,c,g</sup> [✉](#) ...

[Show more](#)

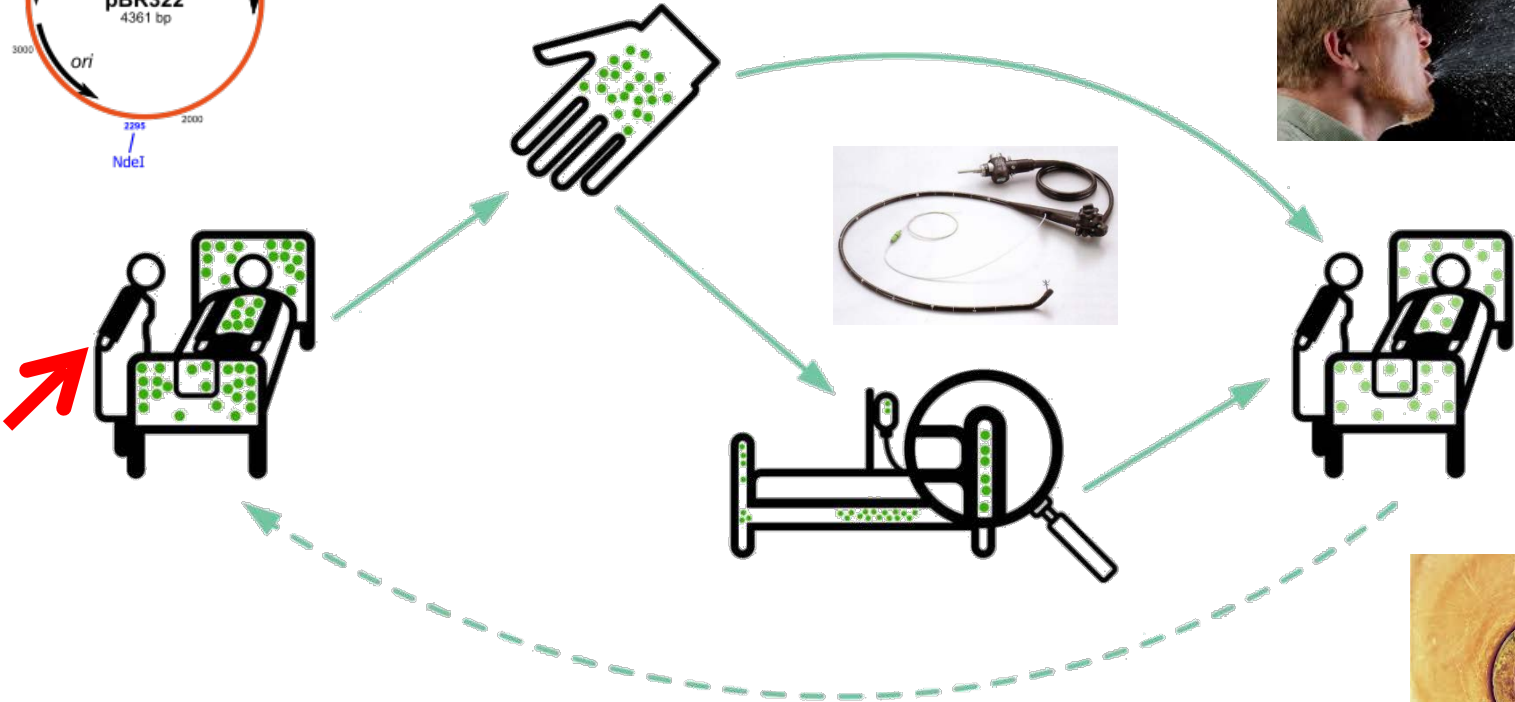
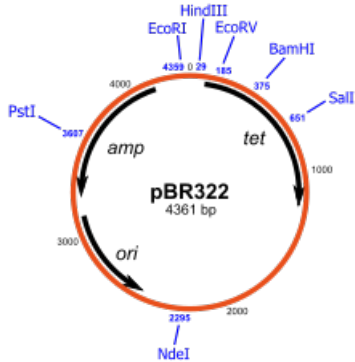
	CRE		CPE	
	Prevalence (%) [95% CI]	P	Prevalence (%) [95% CI]	P
Overall	0.78 [0.21; 1.62]	<0.01	0.74 [0.41; 1.15]	<0.01
Setting				
Healthcare	1.17 [0.29; 2.51]	<0.01	1.06 [0.59; 1.64]	<0.01
Community	2.00 [0.43; 4.50] <sup>a</sup>	–	0.11 [0.00; 0.79]	0.15

# CRE/CPE in the community

Country/Region	Study (year; first author)	Setting & population	Sample size	Screening method	CPE prevalence	Dominant carbapenemase(s)
India	Indian J Med Microbiol (2022; Nasheed Arum et al.)	Healthy community volunteers in Chennai, Hyderabad, Mumbai	1,000	chromID CARBA SMART → CARBA NP → multiplex PCR	6.1%	NDM-1 (28 isolates) and OXA-48 (33)
Pakistan (Rawalpindi)	J Antimicrob Chemother (2011; Perry et al.)	outpatients at 2 military hospitals; community signal from outpatients	200	Colorex KPC vs ID Carba; phenotypic + PCR	Overall 18.5%; outpatients 13.8%	NDM-1 only detected
Pakistan (Rawalpindi)	PLOS One (2022; Habib et al.)	Rectal swabs at hospital admission (community baseline), then follow-up during stay	306 (admission screens)	Ertapenem-supplemented agar; WGS	14.4% at admission	Predominantly NDM-5; also OXA-181/OXA-232
Spain (Madrid)	J Clin Microbiol (2012; Gijón et al.)	Mixed hospitalized vs. non-hospitalized samples; community signal from non-hospitalized	1,100	Enrichment with imipenem → MacConkey; phenotypic assays; gene typing	Non-hospitalized: 0.4% (overall 1.1%)	Mostly VIM-1
United Kingdom	J Hosp Infect (2025; Almadhoon et al., systematic review)	Community carriage point-prevalence (pooled across UK surveys)	N=2,630 (community subset)	Various (culture±PCR), systematic meta-analysis	0.11% (95% CI 0.00–0.79)	Varies by study
Ethiopia (Addis Ababa)	BMC Microbiol (2024; Abera et al.)	Healthy community participants (Gulele sub-city)	261	Culture; phenotypic carbapenemase tests; PCR	0.8% CP-CRE	Not fully specified; ESBL genes (blaTEM, blaCTX-M) prevalent
Vietnam (Ha Nam, rural)	Lancet Regional Health–Western Pacific (2025; van Wijk et al.)	Household cross-sectional rural community	1,502	Culture on meropenem/ceftazidime media	CRE: 1.9%	—

How do we stop it?

# Transmission modes



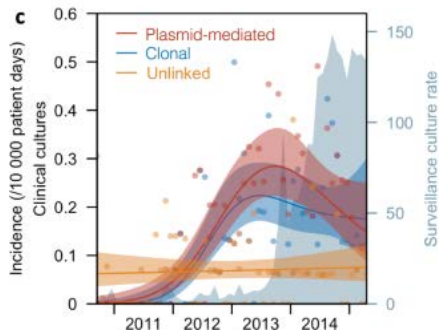
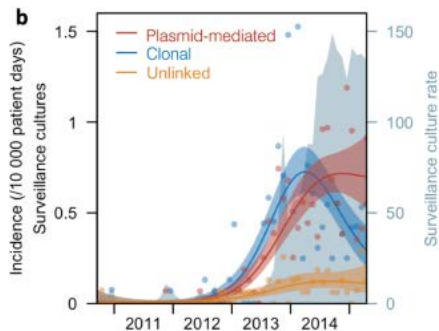
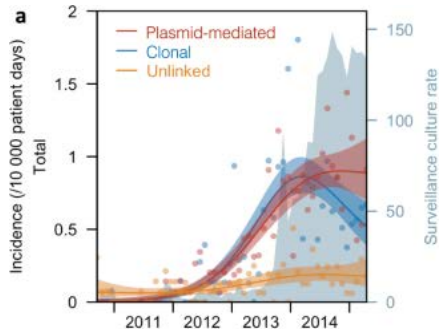
# Promiscuous plasmids

- Inter-species plasmid transfer of AMR genes was investigated in the 1970s regarding [gentamicin-resistance](#).<sup>1</sup>
- 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.<sup>2</sup>
- In [one plasmid outbreak](#),<sup>3</sup> 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.<sup>4,5</sup>
- **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)

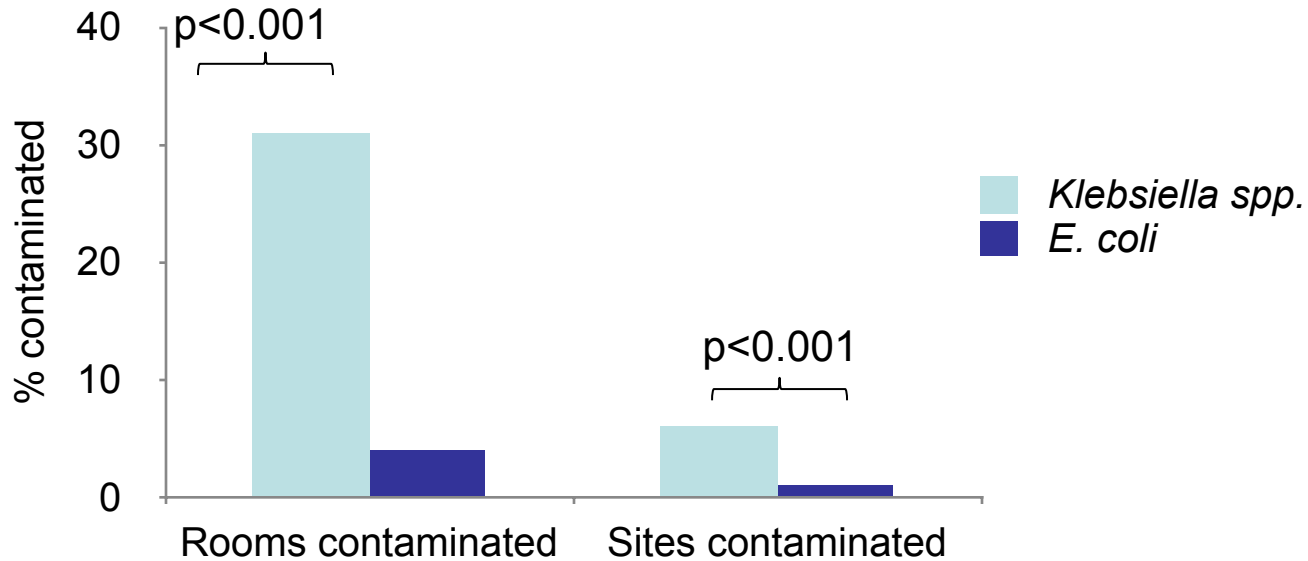
## Significant risk factors for plasmid-mediated spread of CPE:

- **none**

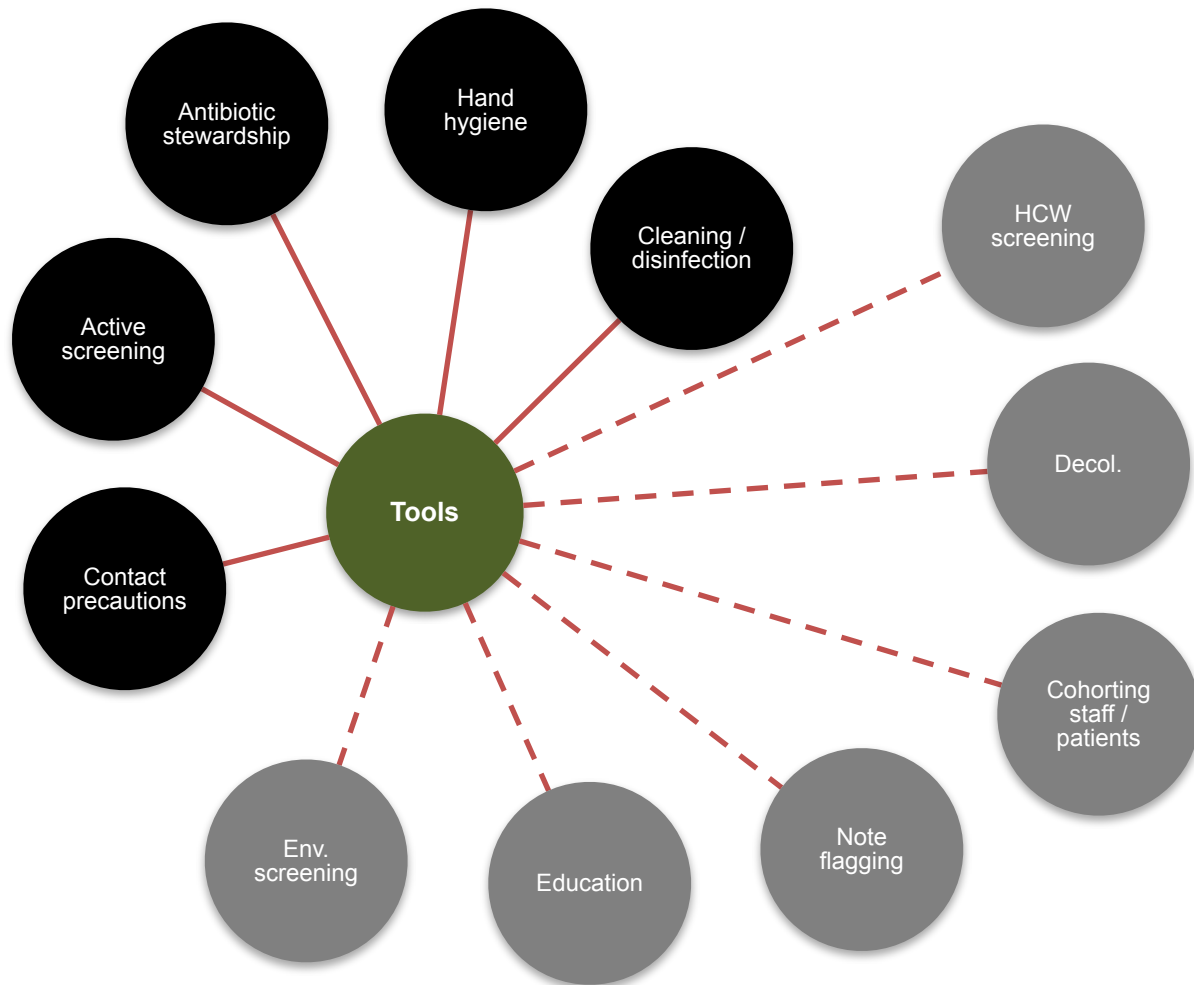
# Transmissibility / fitness

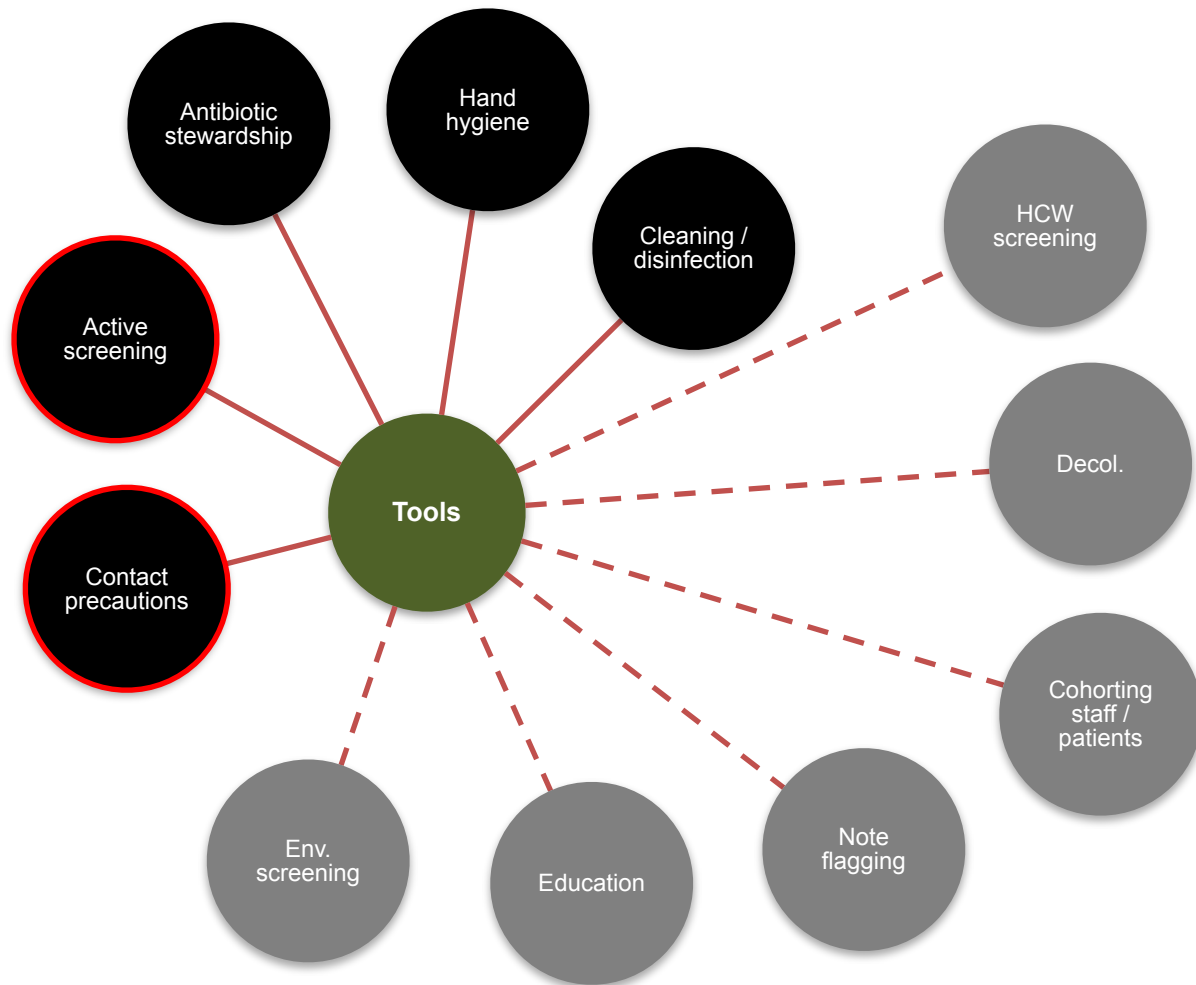
- *Klebsiella* species **3.7x** more transmissible than *E. coli* in the ICU.<sup>1</sup>
- *K. pneumoniae* seems to be more environmental than *E. coli*.<sup>2,3</sup>

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).<sup>2</sup>



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.





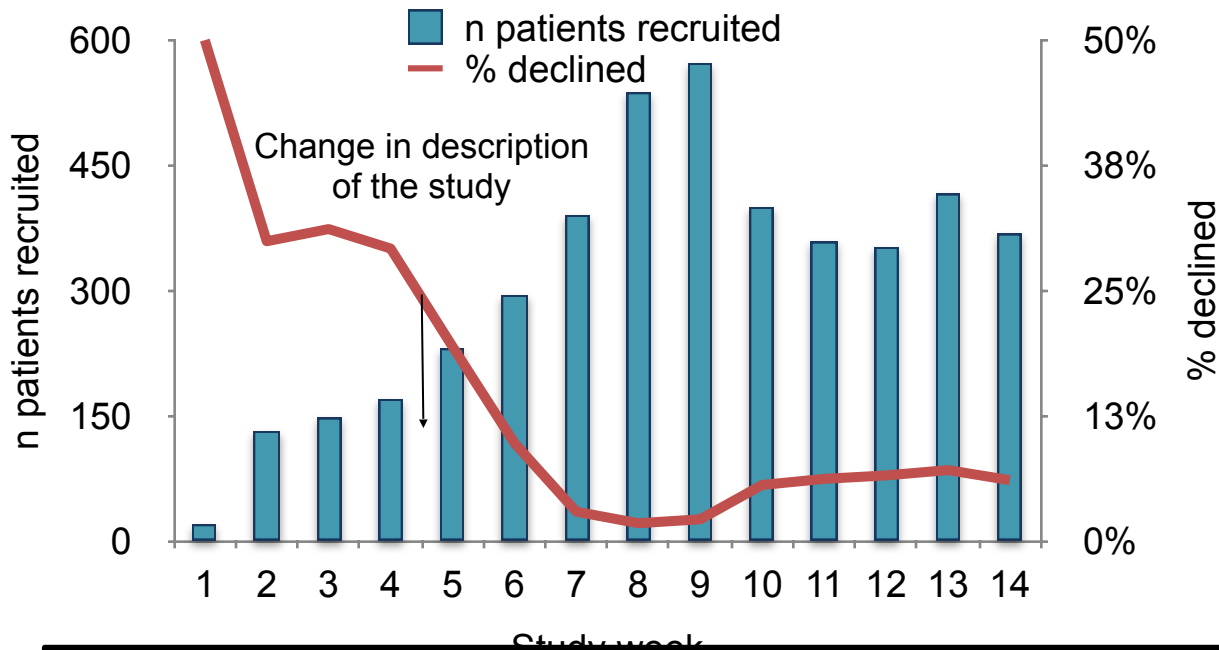
# Who do I screen?

[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.”

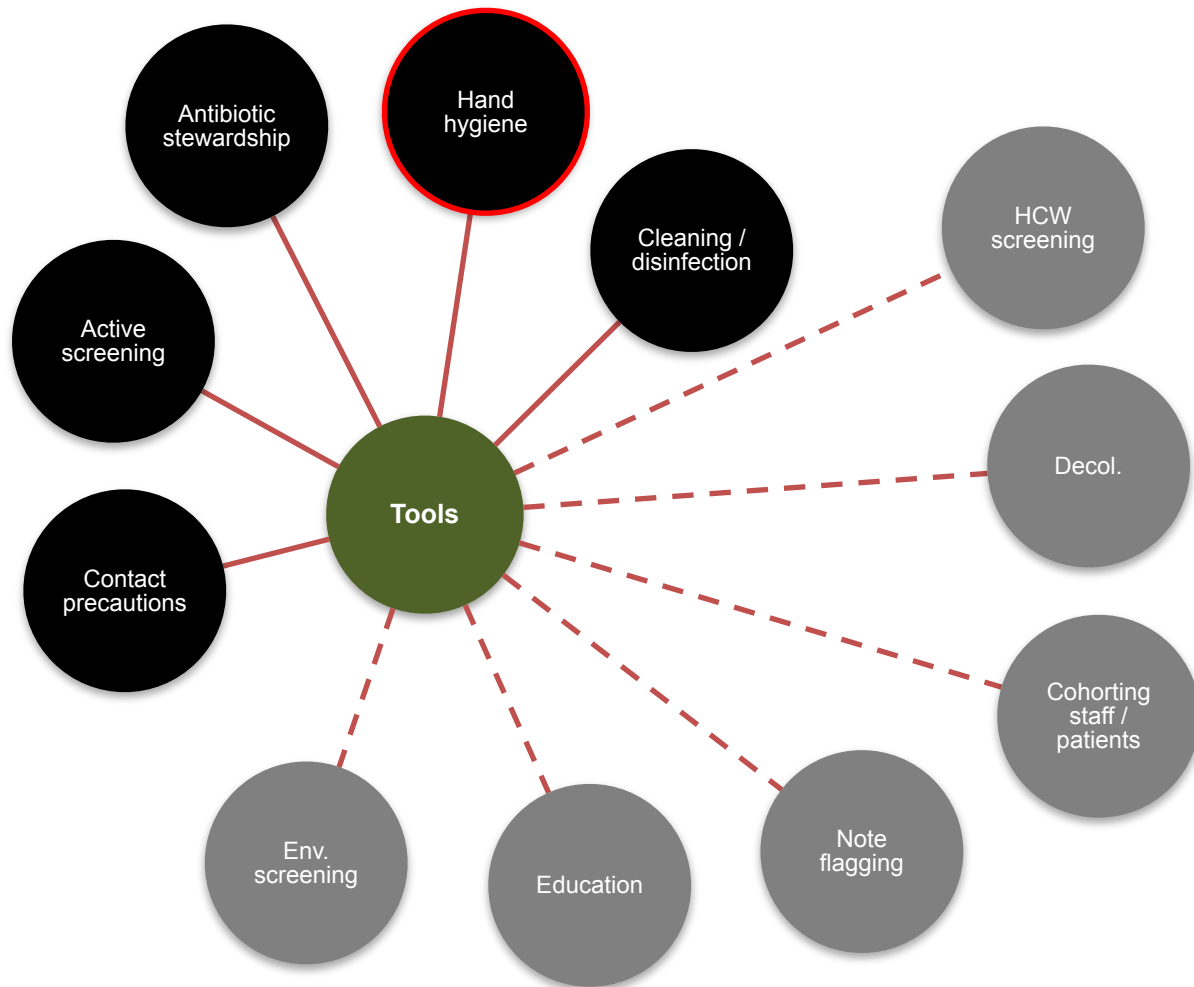
The change in study description results in a significant reduction in decline rate, from 31.9% of 869 patients to 7.6% of 3690 patients ( $p < 0.001$ )

# Colonisation often precedes infection for MDROs

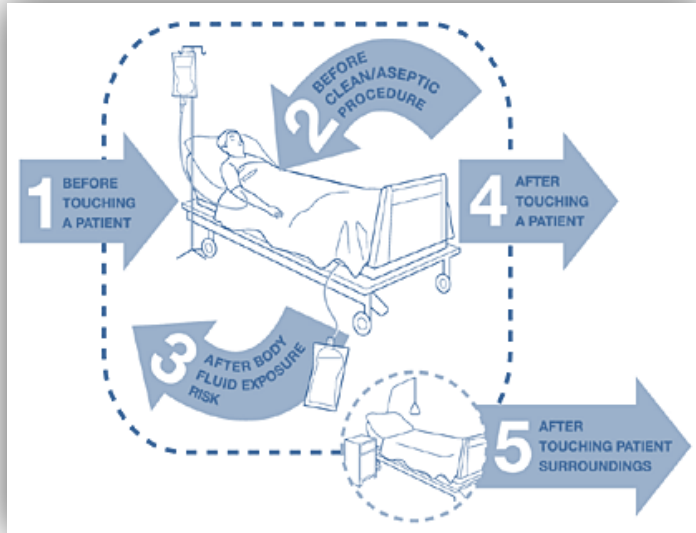
Meta-analyses of subsequent infection in patients first identified as colonised with CPE/VRE.

		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)
	<i>E. coli</i>	7	133/3098	0·08 (0·04–0·14)	6	46/3042	0·04 (0·01–0·10)
	<i>K. pneumoniae</i>	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)

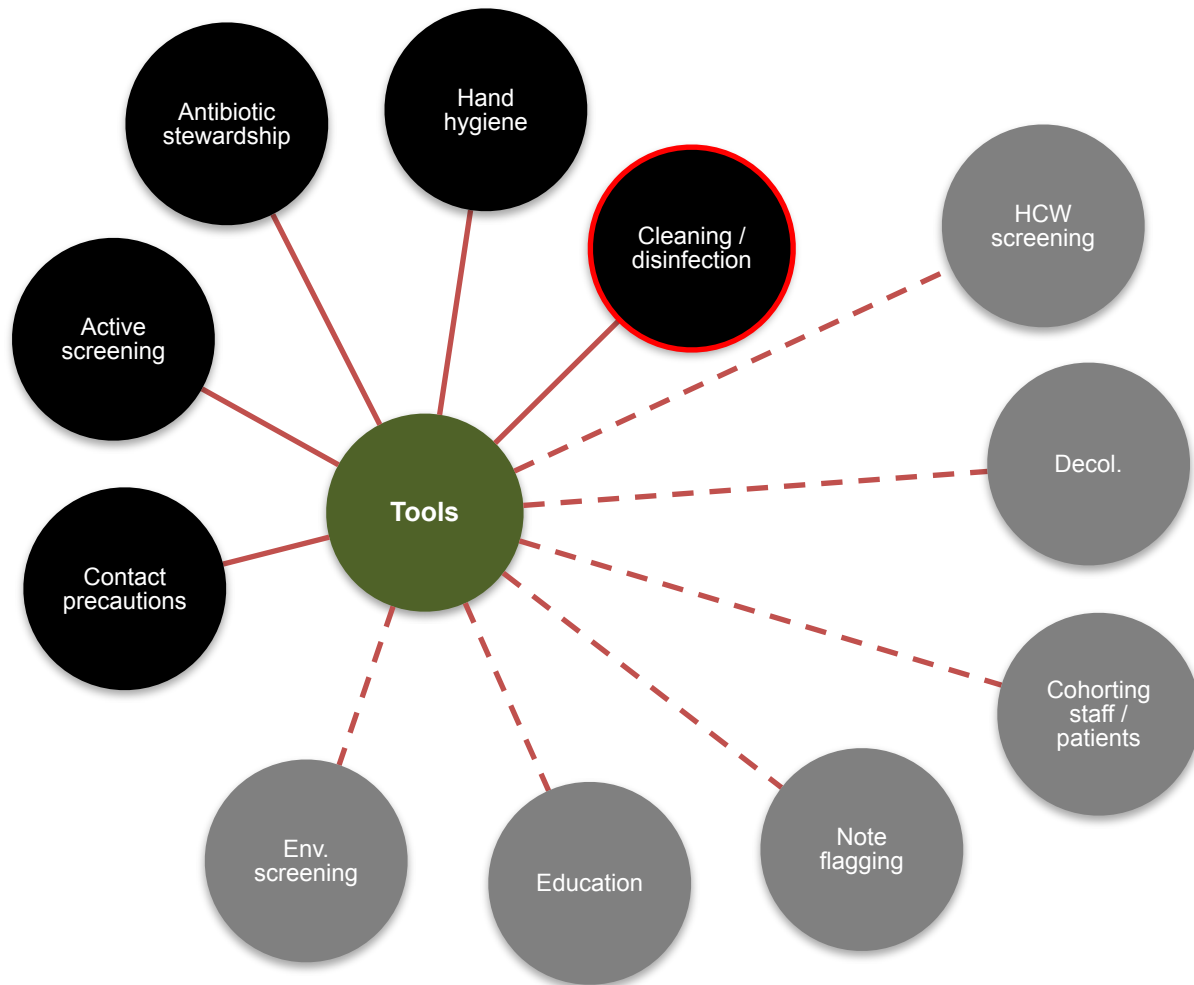
Incidence for CP-CRE was 26% (95% CI 19–35)

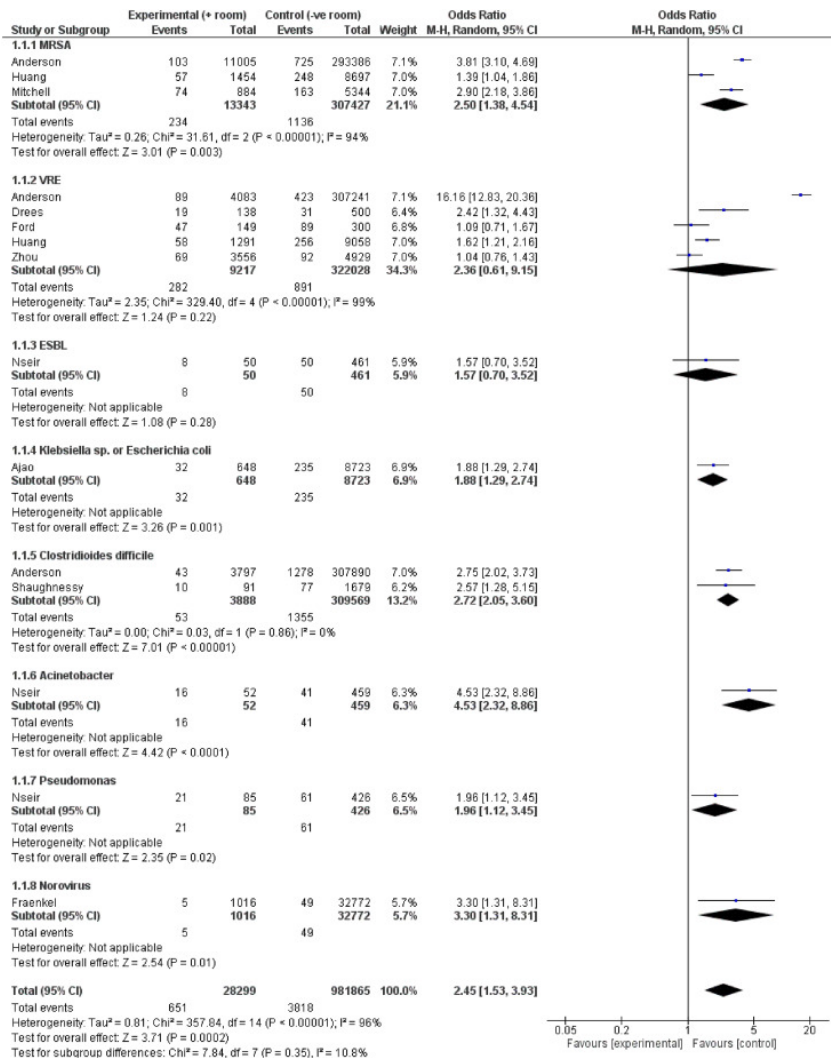


# Contaminated hands



40%





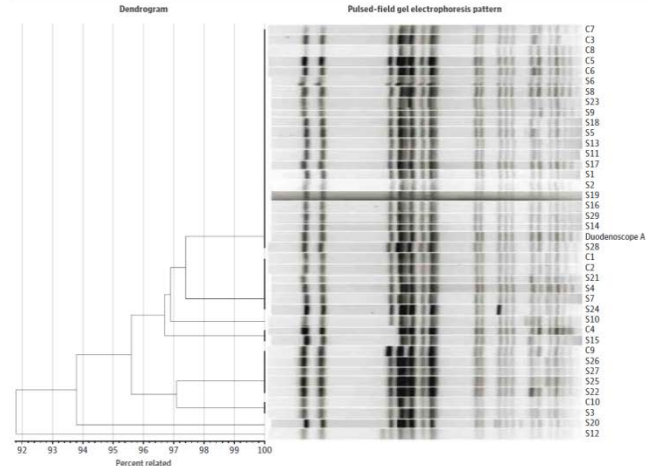
# The MDRO status of the prior room occupant influences acquisition risk

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

# When medical device decon fails...

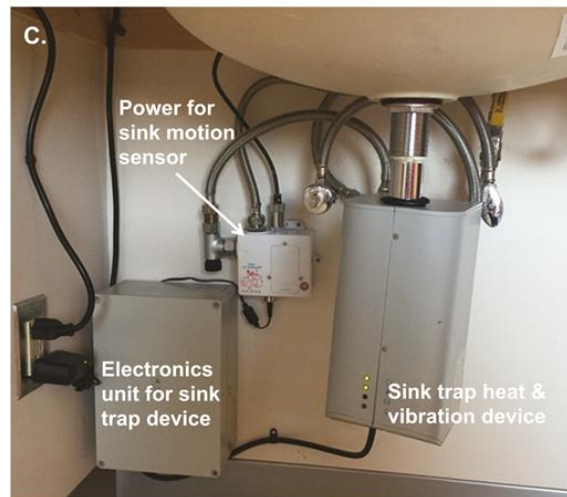
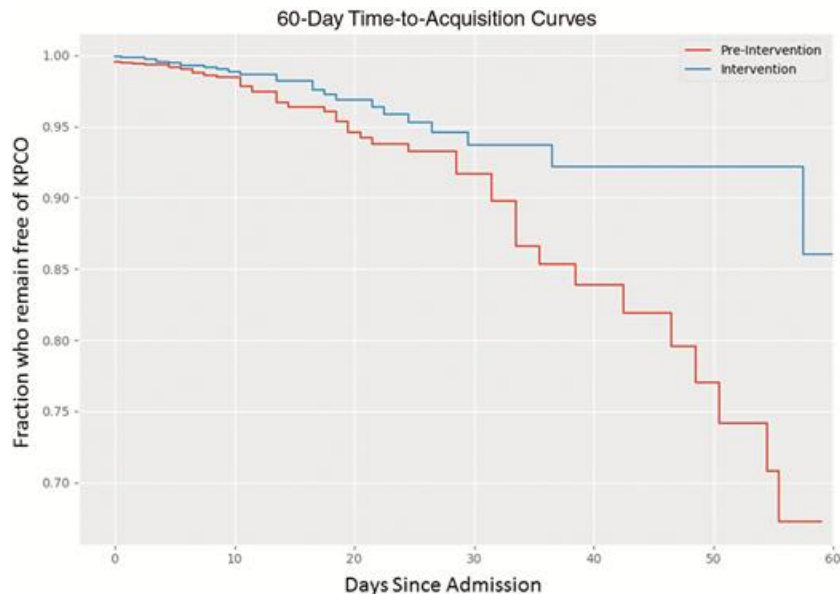
- 39 patient CRE outbreak in 2013 in Illinois.<sup>1</sup>
- Odds ratio for duodenoscope exposure in case patients 78 (95% CI 6-1008).
- No breakdown in compliance with decon procedures; has prompted a global review and change in the way that these devices are decontaminated.<sup>2</sup>
- *Meticulously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

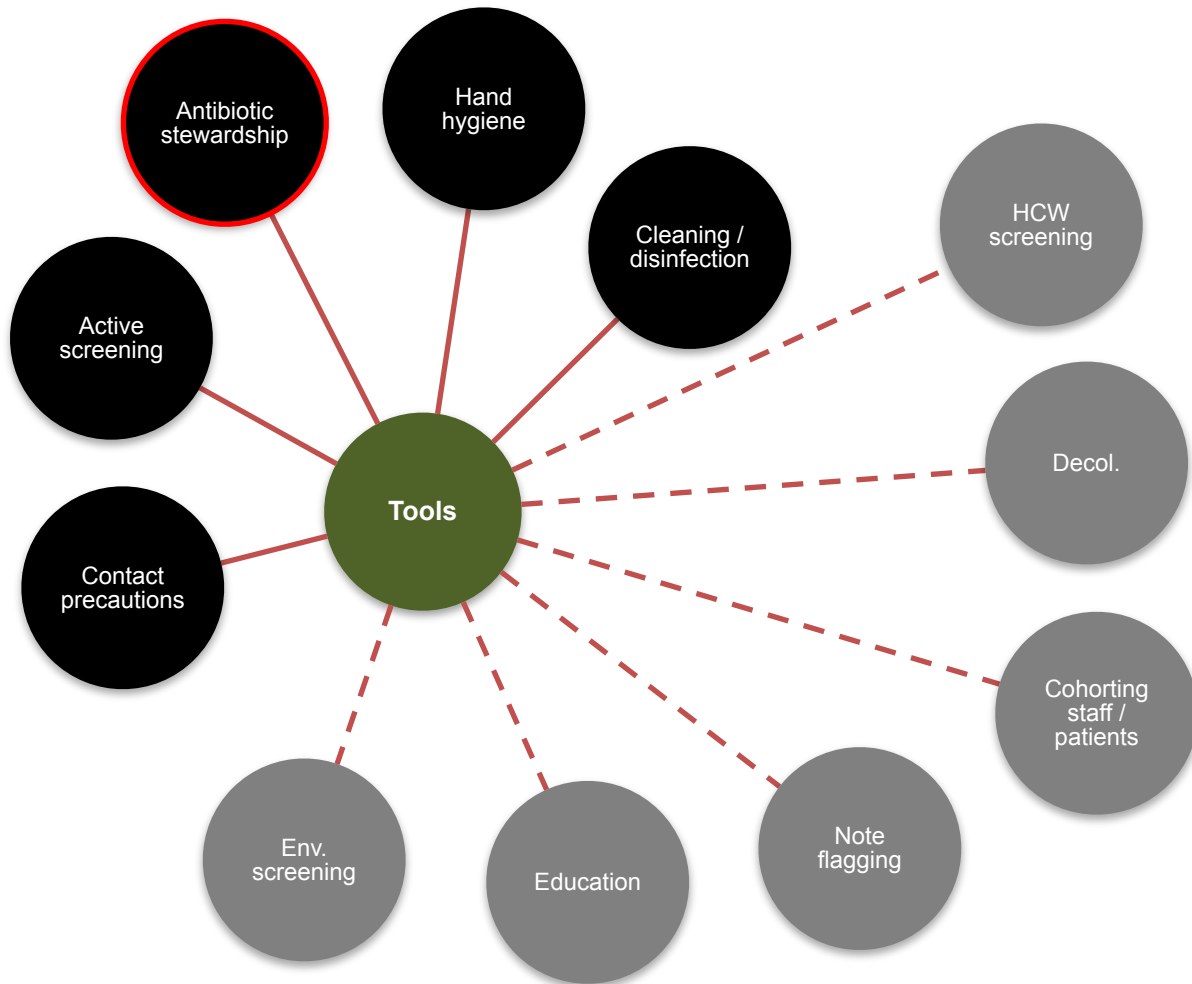


1. Epstein *et al.* *JAMA*. 2014;312:1447-55.
2. Rutala & Weber. *Am J Infect Control* 2016;44 (Supl):e47-51

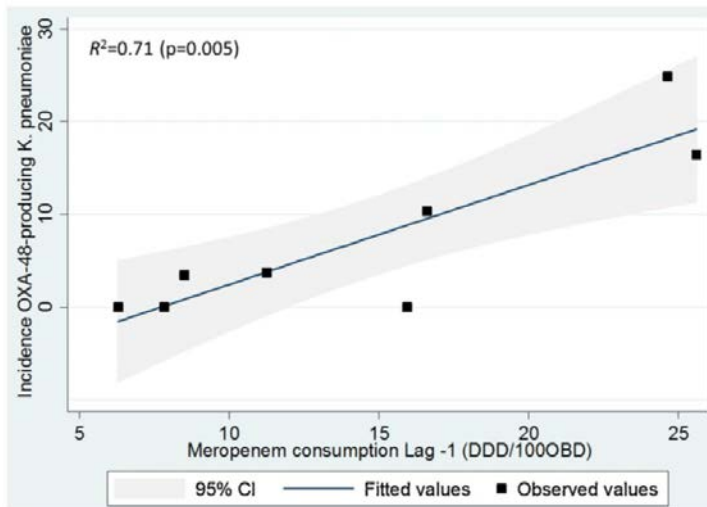
# Contaminated sinks / drains

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





# Can we forecast a CPE storm?



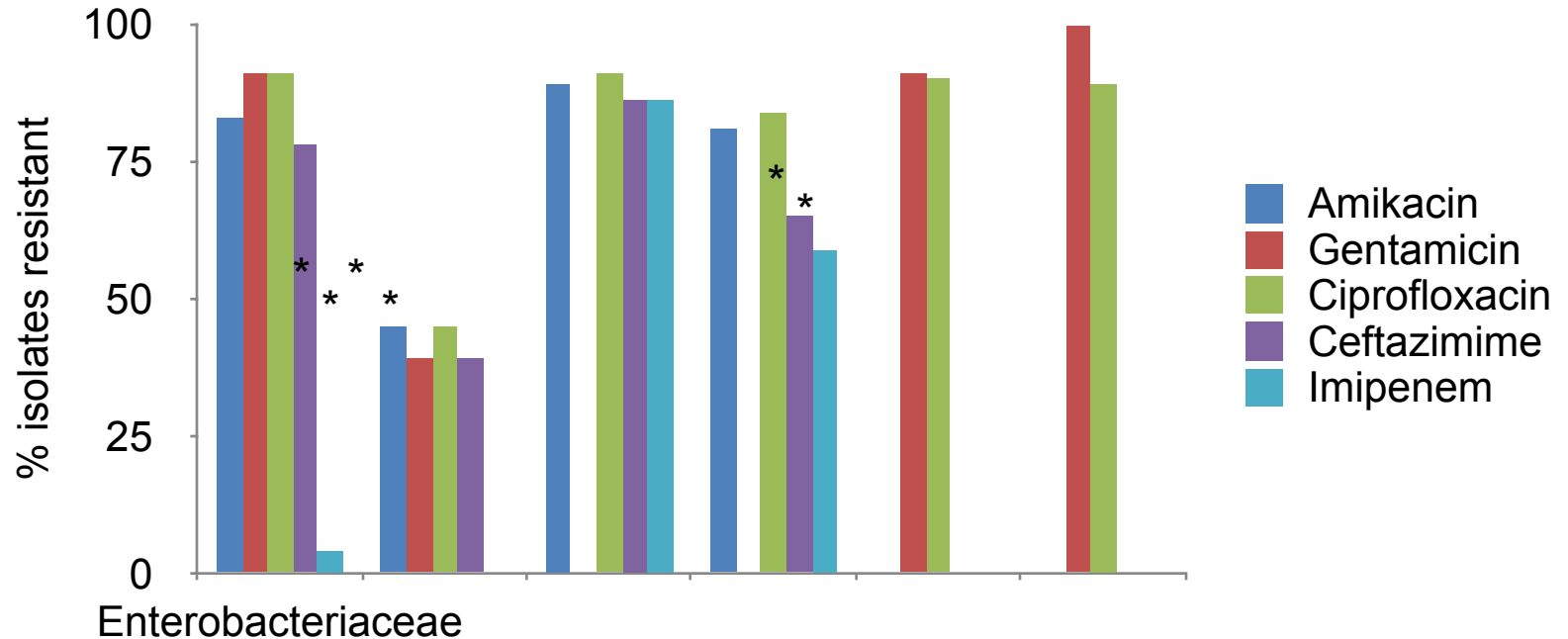
- Could we find and implement an “alert” level of carbapenem use?
- The paper reports that a stewardship intervention brought the CPE outbreak under control – but also implemented ‘case isolation, screening of contacts, barrier nursing and other infection control interventions’.
- Study focussed only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

*What drives carbapenem resistance?*

*The use of meropenem in the previous year plotted against the incidence rate of OXA-48-producing K. pneumoniae*

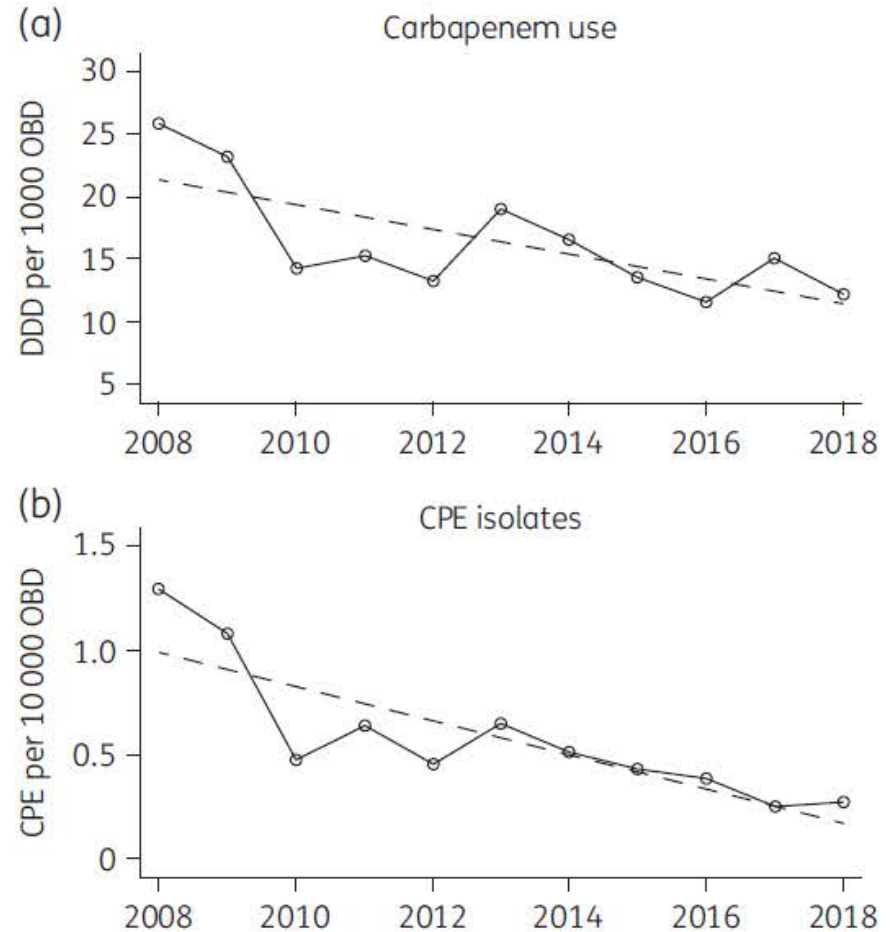
# Antibiotic use

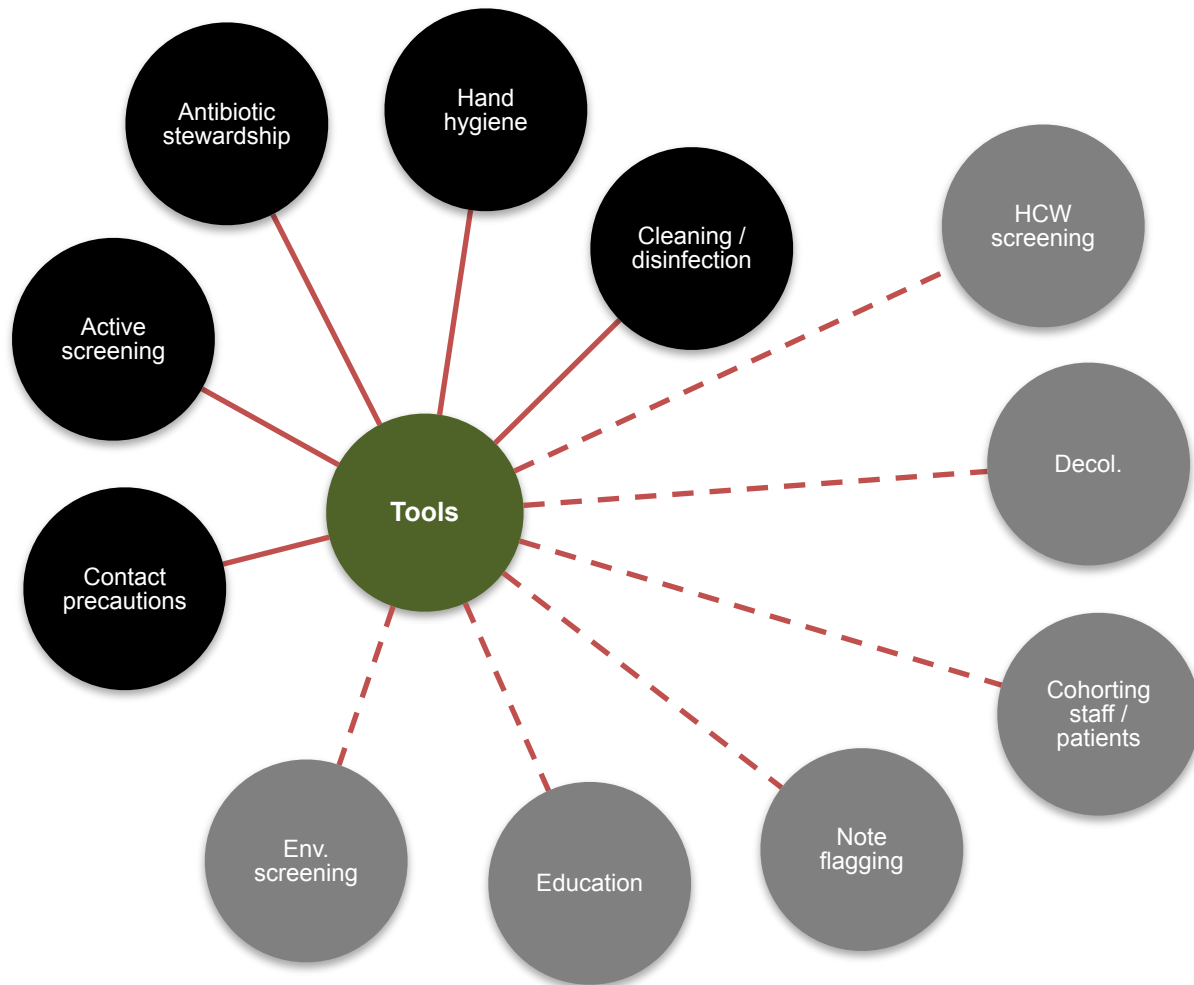
Evaluating impact of 6 month antimicrobial stewardship intervention on an ICU by comparing bacterial resistance for matched 6 month periods either side of intervention.



# Antibiotic use

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





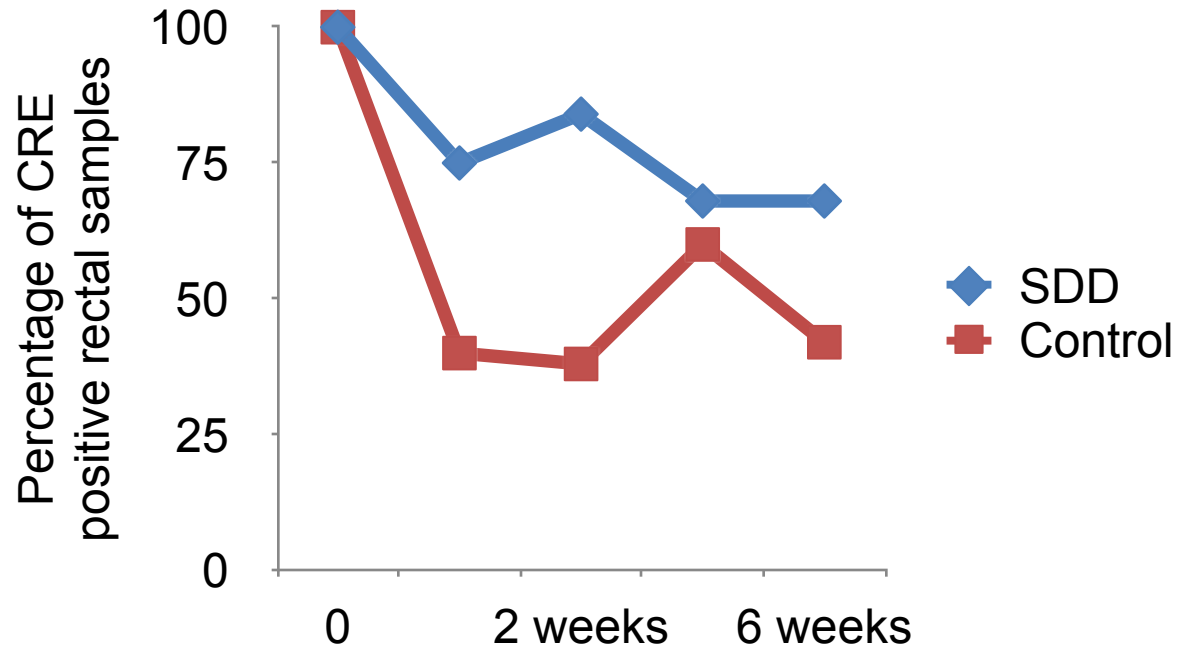
# Deisolation?

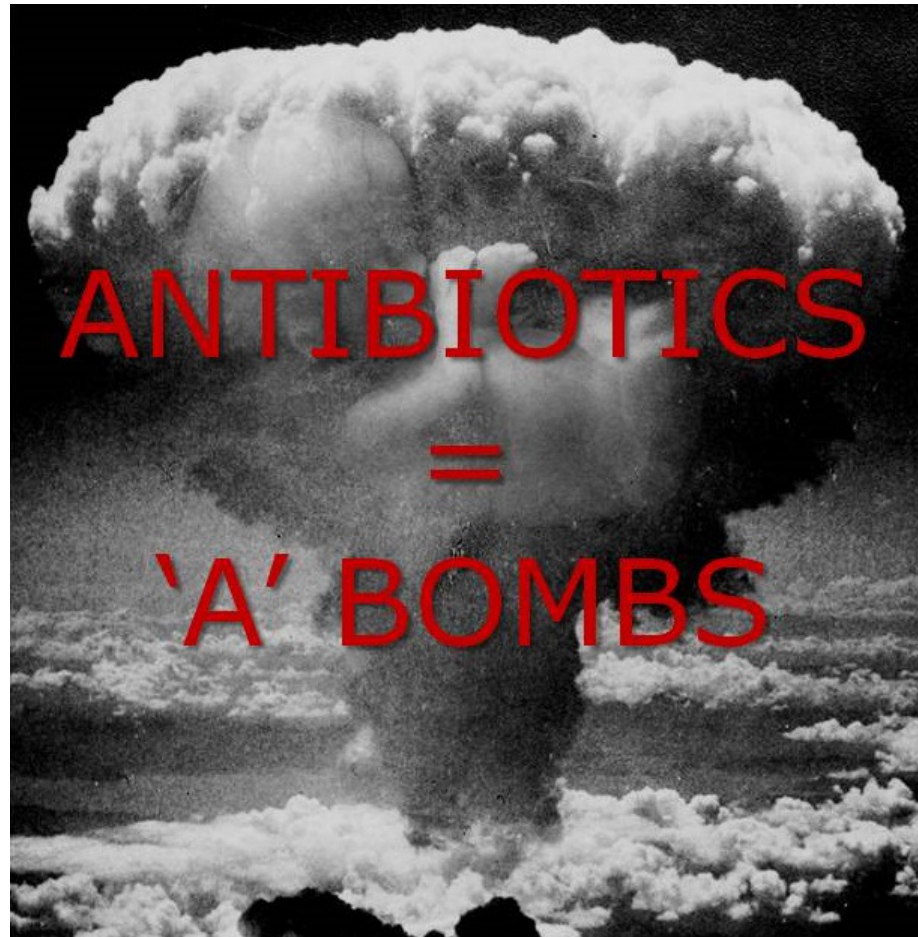
Author	Year	Setting	N pts	Organism	Duration of colonization
Bird <sup>1</sup>	1998	Elderly care facilities, Scotland	38	ESBL <i>K. pneumoniae</i>	Mean 160 days (range 7-548)
Pacio <sup>2</sup>	2003	Long term care facility, USA	8	Resistant Gram-negative rods	Median 77 days (range 47-189)
Zahar <sup>3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





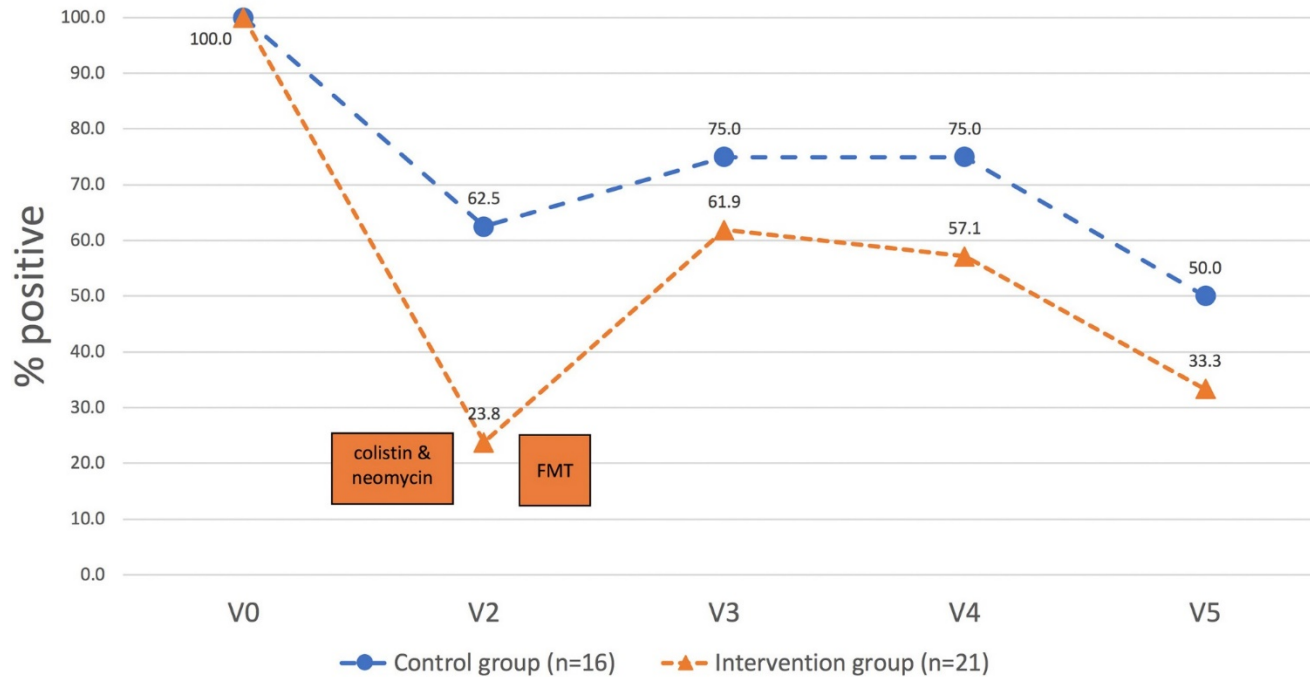
ANTIBIOTICS

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'A' BOMBS

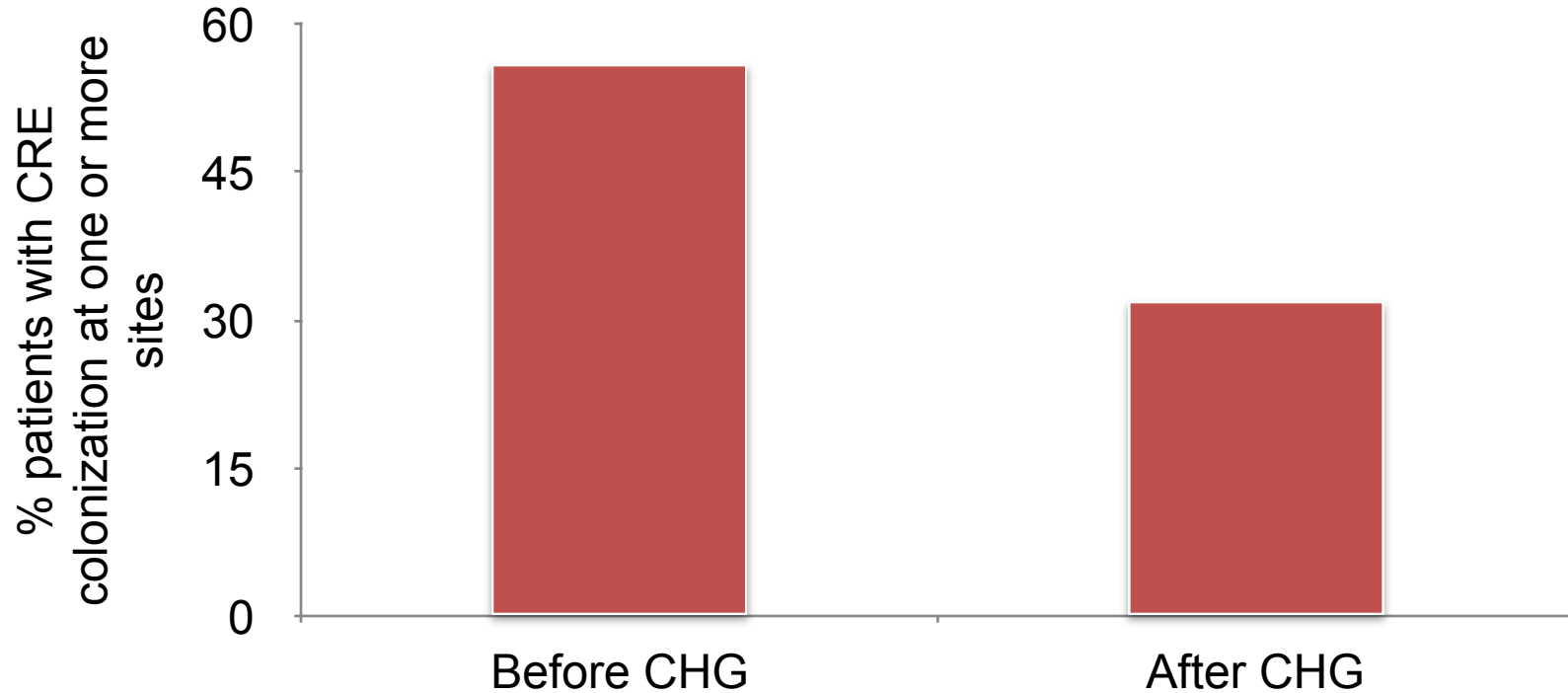
# Decolonisation using FMT

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

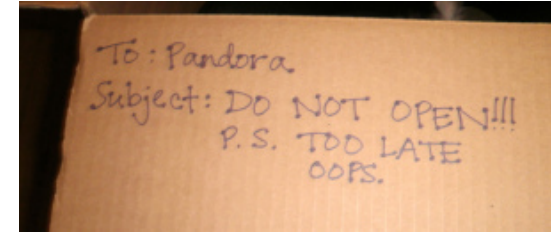


# Chlorhexidine – efficacy

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



# Colonised staff?



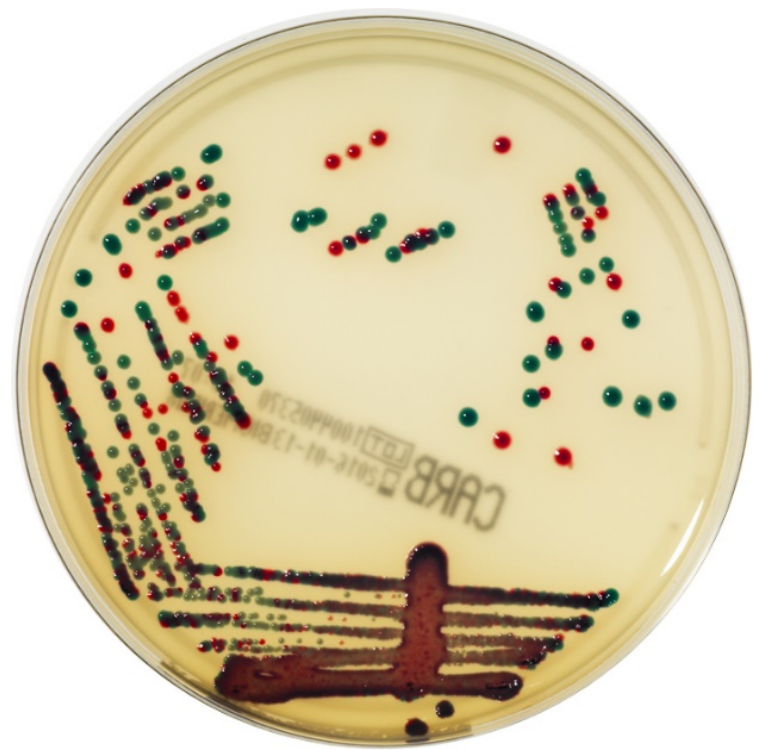
## Multidrug-resistant organism growth from perirectal swabs

Culture result	Healthcare personnel participants <sup>a</sup> (n = 379) n (%)	Control participants <sup>a</sup> (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  $\beta$ -lactamase; MDRO, multidrug-resistant organism.

<sup>a</sup> Includes participants who did not submit questionnaires.

# Carbapenem-resistant Enterobacterales in healthcare and community settings



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