


Rising to the Challenge of Multidrug-Resistant Gram-Negative Bacteria
Dr. Jon Otter, PhD FRCPATH, Imperial College Hospitals NHS Trust
A Webber Training Teleclass

Rising to the challenge of multidrug-resistant Gram- negative bacteria

Jon Otter, PhD FRCPATH
Imperial College Hospitals NHS Trust

Hosted by Prof. Jean-Yves Maillard
Cardiff University, Wales

Imperial College Healthcare 
NHS Trust

www.webbertraining.com

December 10, 2015

**THE END OF
ANTIBIOTICS IS NIGH**

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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



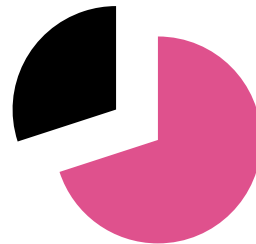
"The rise of antibiotic-resistant bacteria, however, represents a serious threat to public health and the economy."
 Barack Obama, President USA

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Rising threat from MDR-GNB



% 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>	CPO
Enterobacteriaceae	<i>Klebsiella pneumoniae</i> <i>Escherichia coli</i> <i>Enterobacter cloacae</i>	

CPE

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

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Enterobacteriaceae vs. non-fermenters

Share	Differ
Gram stain reaction	Risk factors & at-risk population
Concerning AMR	Potential for epidemic spread
	Infection profile & mortality
	Prevalence
	Colonisation site & duration
	Transmission routes
	Resistance profile & mechanisms

What's the problem? Resistance

30 Jun 2014 00:00	BC - Blood culture	AICU - AICU	CNS - Coagulase Negative Staphylococcus
30 Jun 2014 00:00	ASC - Ascitic fluid	AICU - AICU	GPC - Unidentified Gram positive coccus
			SE - Staphylococcus epidermidis
			KP - Klebsiella pneumoniae
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
		COM - Cefuroxime	R
		ERT - Ertapenem	R
		GEN - Gentamicin	R
		MER - Meropenem	R
		TAZ - Pip/Tazobactam	R
		TGC - Tigecycline	R
		TRI - Trimethoprim	R

Courtesy of Pat Cattini

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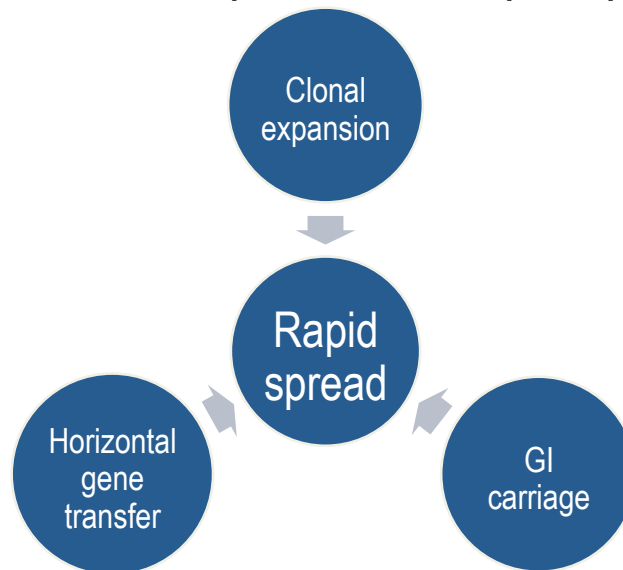
What's the problem? Mortality

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

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

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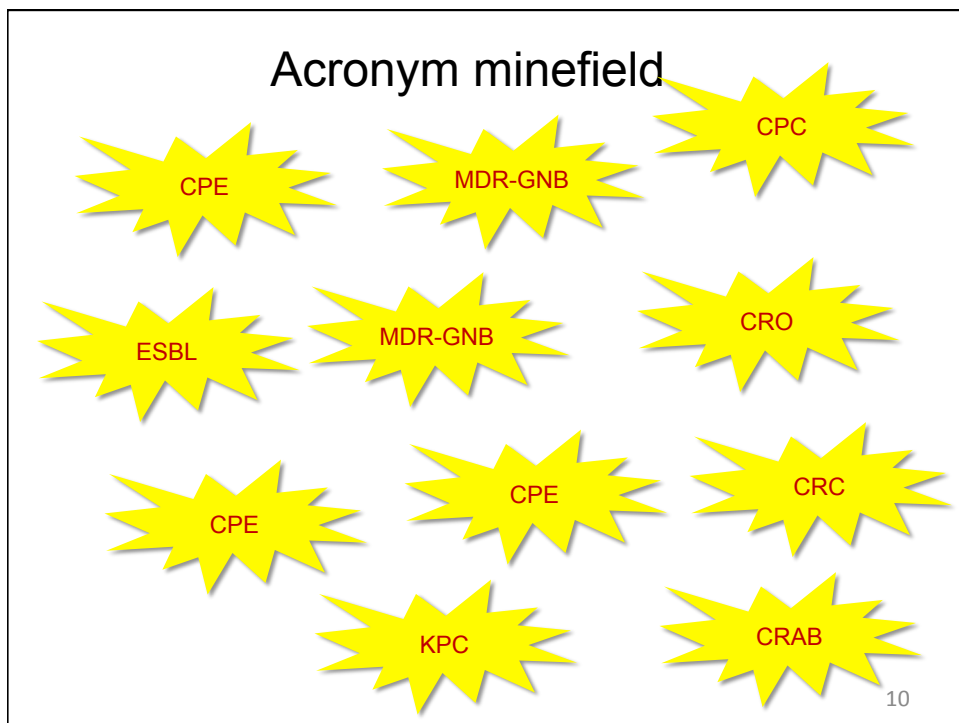
What's the problem? Rapid spread



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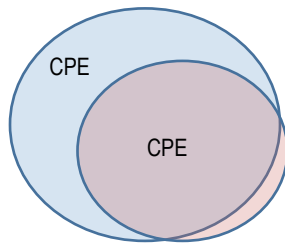
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What are CPE?

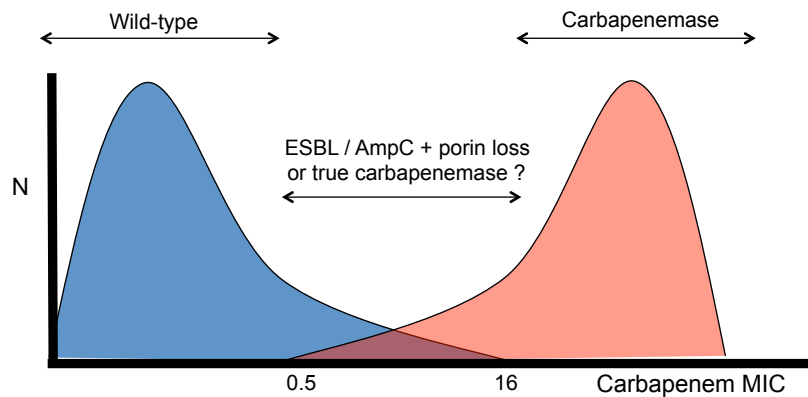
Carbapenem-resistant Enterobacteriaceae (CPE) – Enterobacteriaceae that are resistant to carbapenems by any mechanism.

Carbapenemase-producing Enterobacteriaceae (CPE) – Enterobacteriaceae that are resistant to carbapenems by means of an acquired carbapenemase.



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When CPE is not CPE



Courtesy of Dr Katie Hopkins, PHE.

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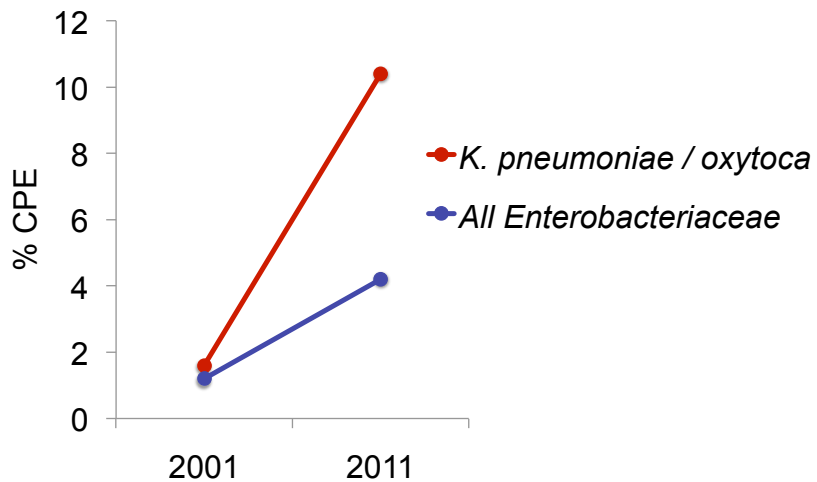
Understanding the enemy

Pathogen	CPE ¹	CPAB ²	MRSA	VRE	<i>C. difficile</i>
Resistance	+++	+++	+	+	+/-
Resistance genes	Multiple	Multiple	Single	Single	n/a
Species	Multiple	Single	Single	Single	Single
HA vs CA	HA & CA	HA (ICU)	HA	HA	HA
At-risk pts	All	ICU	Unwell	Unwell	Old
Virulence	+++	+/-	++	+/-	+
Environment	+/-	+++	+	++	+++

1. Carbapenemase-producing Enterobacteriaceae.
2. Carbapenemase-producing *Acinetobacter baumannii*.

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CPE in the USA

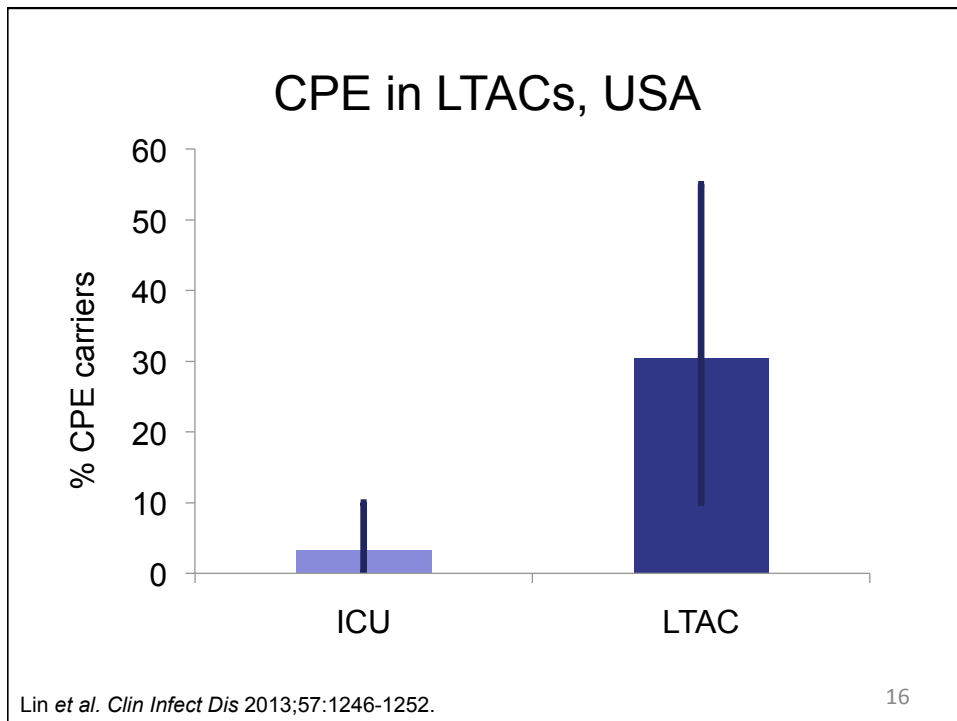
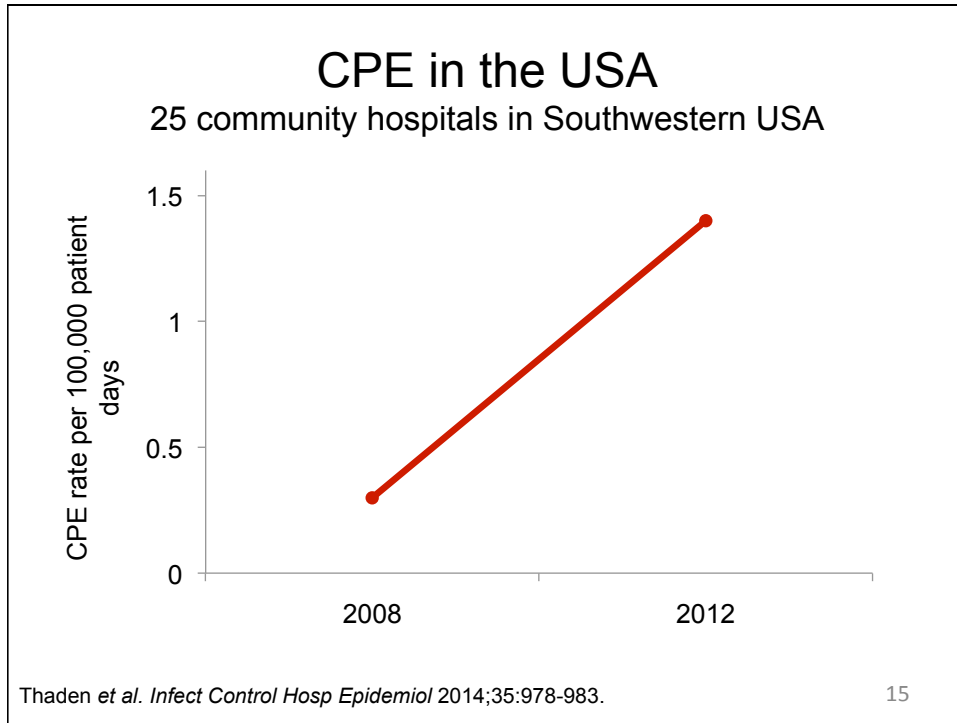


NHSN / NNIS data; *MMWR* 2013;62:165-170.

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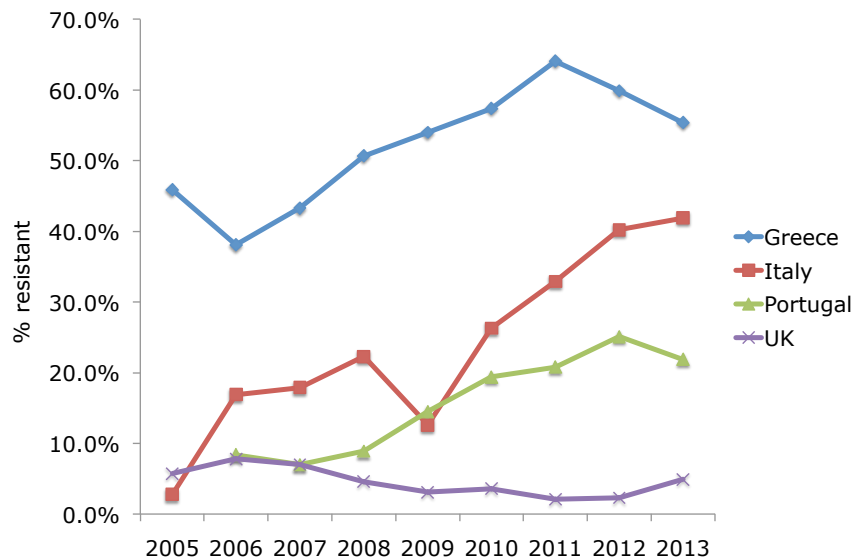
Who's carrying CPE?

Author	Year	Location	Setting	n patients	n carriers	% carriers
Adler ¹	2015	Israel	CPE carriage in post-acute hospitals, 2008	1147	184	16.0
–	–	–	CPE carriage in post-acute hospitals, 2013	1287	127	9.9
Mack	2014	London	'High-risk' inpatients and admissions.	2077	7	0.3
Rai ²	2014	East Delhi, India	Outpatients	242	24	9.9
Zhao ³	2014	Fujian, China	Stool samples from hospitalized patients	303	20	6.6
Birgand ⁴	2014	Paris, France	Patients repatriated or recently hospitalized in a foreign country	132	9	6.8
Kim ⁵	2014	Seoul, Korea	ICU admissions	347	1	0.3
Girlich ⁶	2014	Morocco	Hospitalized patients	77	10	13.0
Lin ⁷	2013	Chicago, USA	Long term acute care hospitals	391	119	30.4
–	–	–	Short stay hospital ICU	910	30	3.3
Villar ⁸	2013	Buenos Aires, Argentina	Non-hospitalized individuals	164	8	4.9
Kothari ⁹	2013	New Delhi, India.	Healthy neonates	75	1	1.3
Day ¹⁰	2013	Pakistan	Patients attending a military hospital	175	32	18.3
Swaminathan ¹¹	2013	New York	All admissions to 7 units, including ICU, of 2 hospitals	5676	306	5.4
Nüesch-Inderbilen ¹²	2013	Zurich, Switzerland	Healthy community residents and outpatients	605	0	0.0
Armand-Lefèvre ¹³	2013	Paris, France	ICU patients	50	6	12.0
Wiener-Well ¹⁴	2010	Jerusalem, Israel	Hospitalized patients	298	16	5.4

For refs see: <http://reflectionsipc.com/2014/12/22/whos-harboring-cre/>

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Invasive multidrug-resistant *K. pneumoniae*



EARS-Net

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Colistin resistance in Italy



Survey of 191 CPE from 21 labs across Italy.

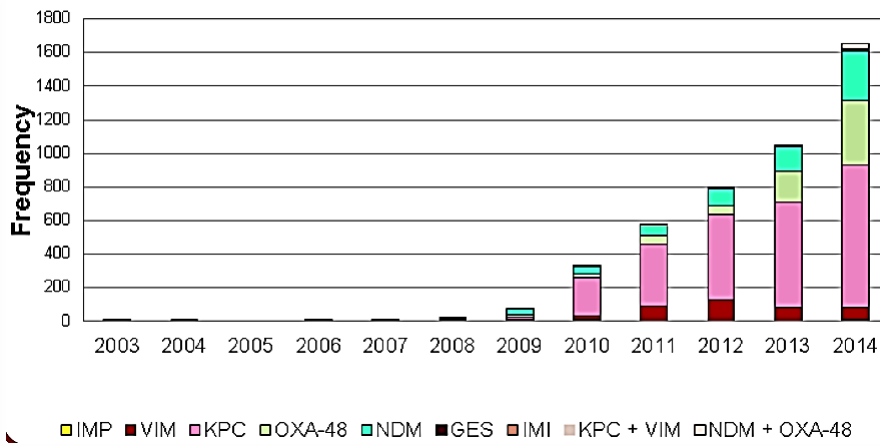
43%

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

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

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Emergence of CPE in the UK



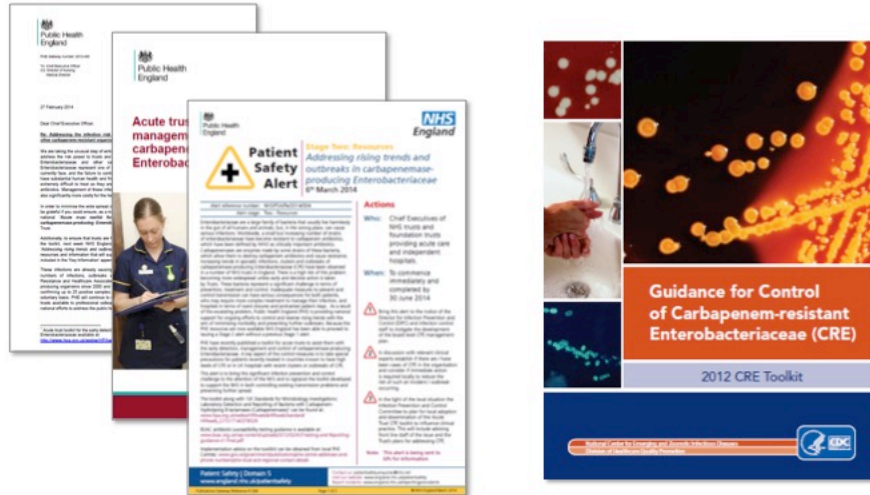
PHE.

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CPE in the UK and US



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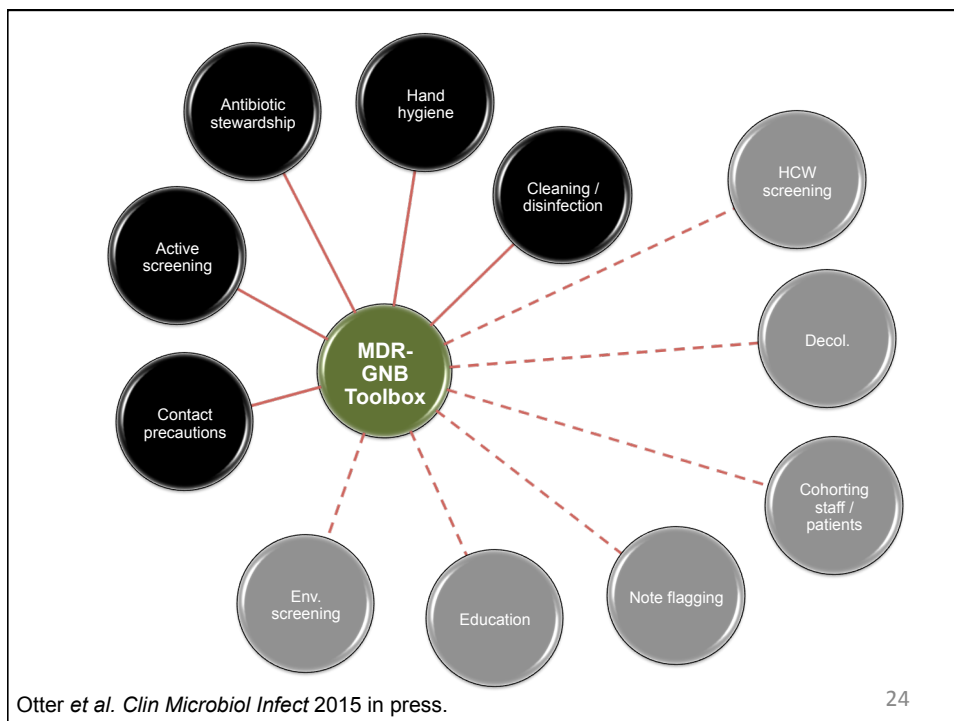
Evidence-free zone

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Guidelines \neq Policy

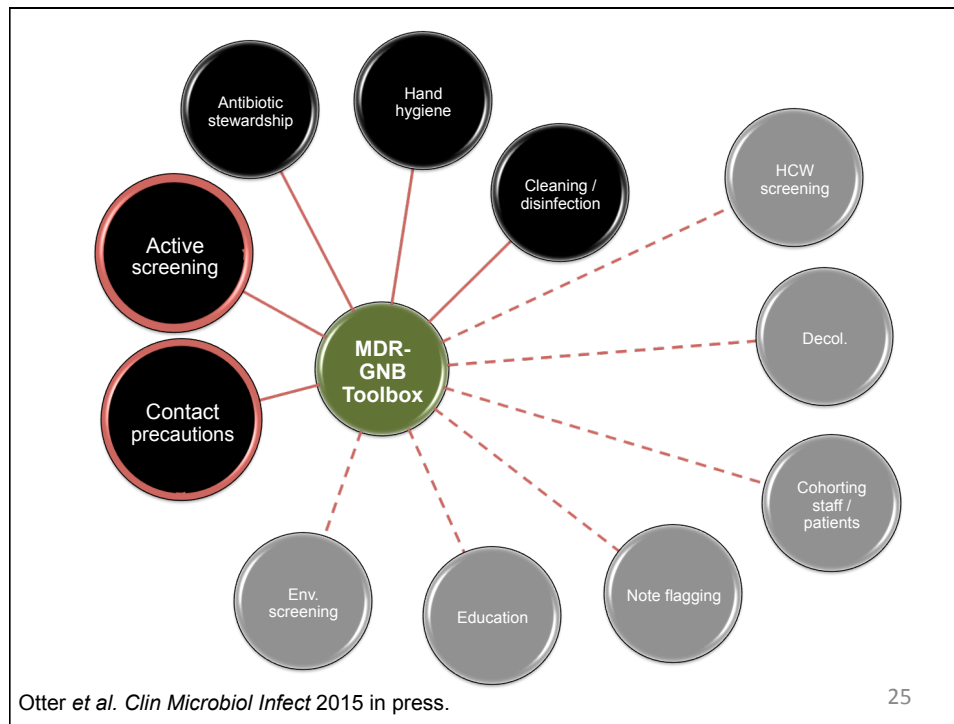
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Who do I screen?

[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.

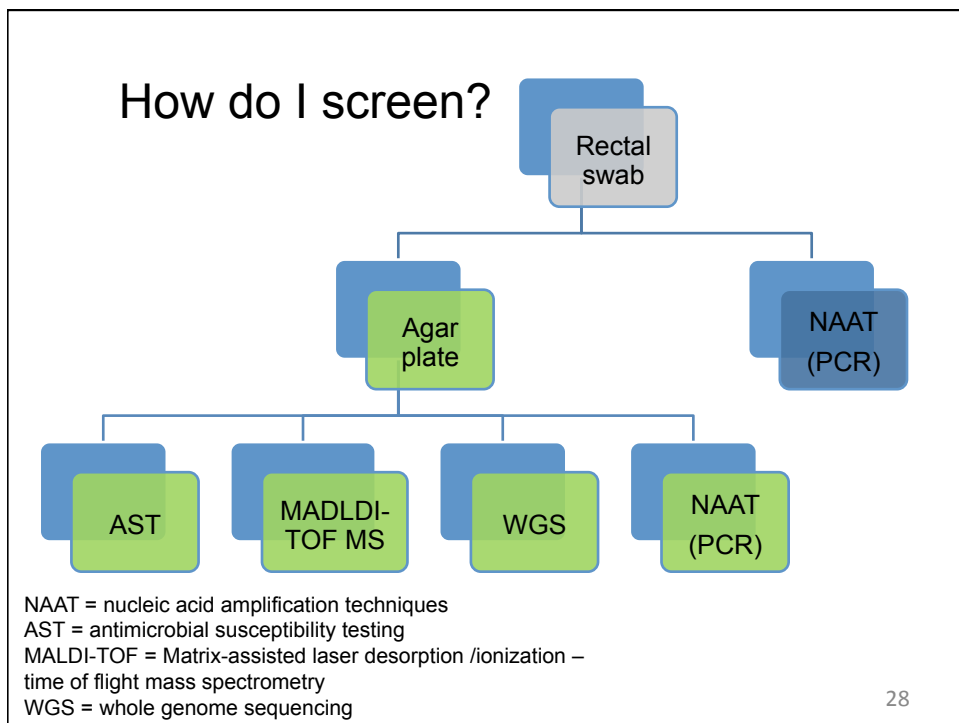
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How do I screen?

- 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'



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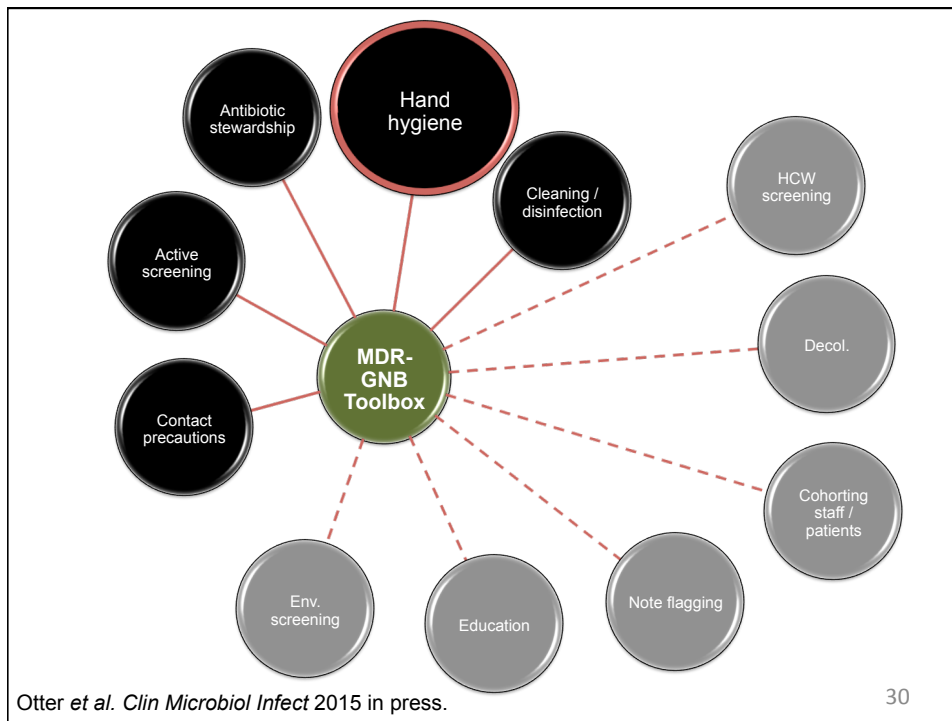
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Does screening and isolation work?

	All MDROs	MRSA	VRE	ESBLs
Baseline trend	–	↑	–	–
Hygiene intervention step-change	–	–	–	–
Hygiene intervention trend change	↓	↓	–	–
Screening step-change	–	–	–	–
Screening trend change	–	↑	–	–
Rapid vs. conventional step-change	↑	–	–	↑
Rapid vs. conventional trend-change	–	–	–	–

[Derde et al. Lancet Infect Dis 2014;14:31-39.](#)

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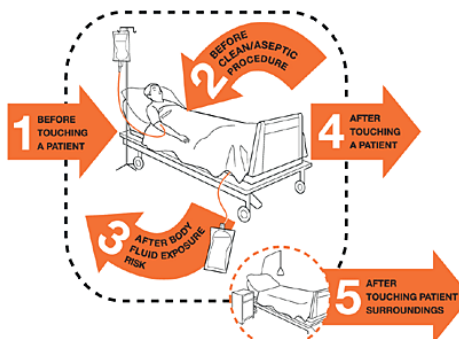
Otter et al. Clin Microbiol Infect 2015 in press.

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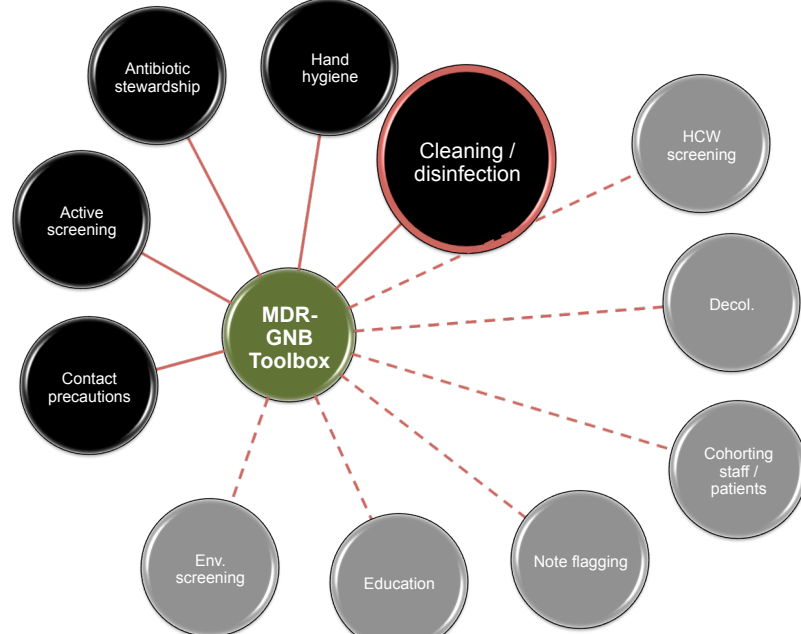
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Hand hygiene



40%
Median hand hygiene compliance
from 95 studies.

Erasmus *et al.* *Infect Control Hosp Epidemiol* 2010;31:283-294. 31



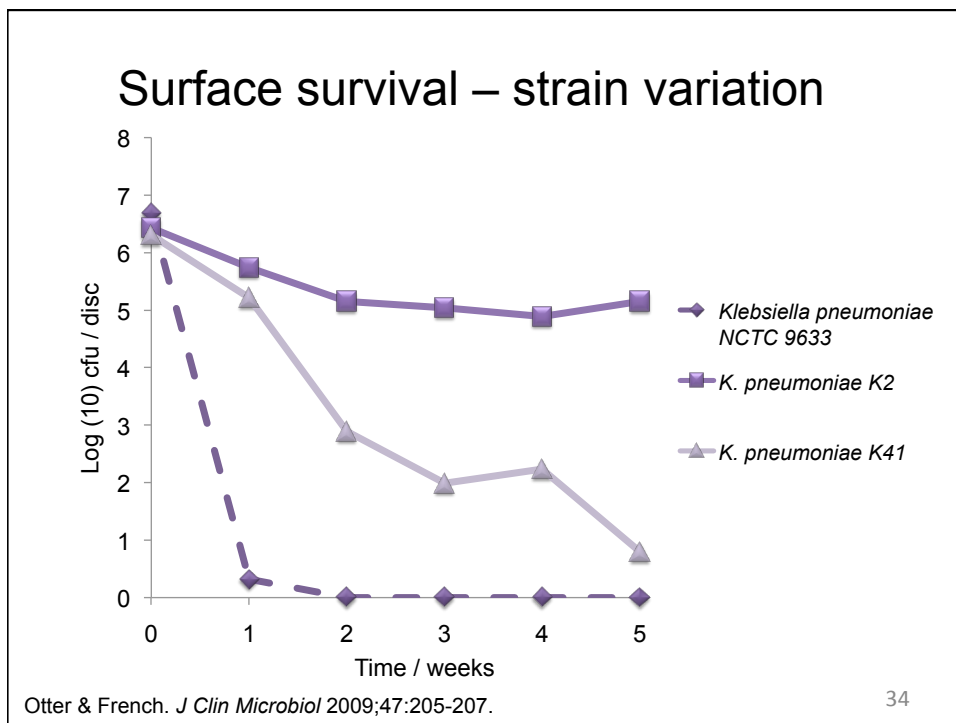
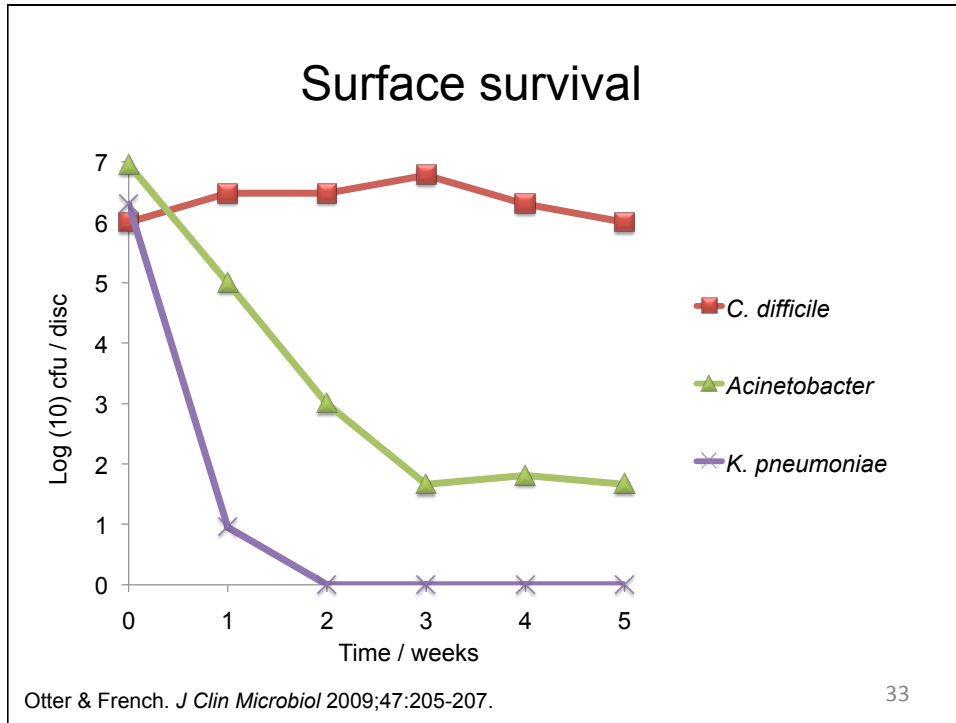
MDR-GNB Toolbox

- Antibiotic stewardship
- Hand hygiene
- Cleaning / disinfection
- HCW screening
- Decol.
- Cohorting staff / patients
- Note flagging
- Education
- Env. screening
- Contact precautions
- Active screening

Otter *et al.* *Clin Microbiol Infect* 2015 in press. 32

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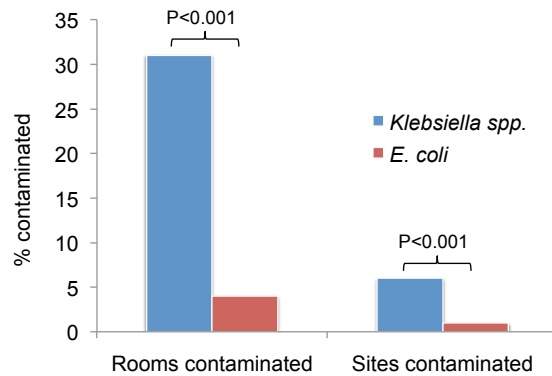


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K. pneumoniae vs. E. coli

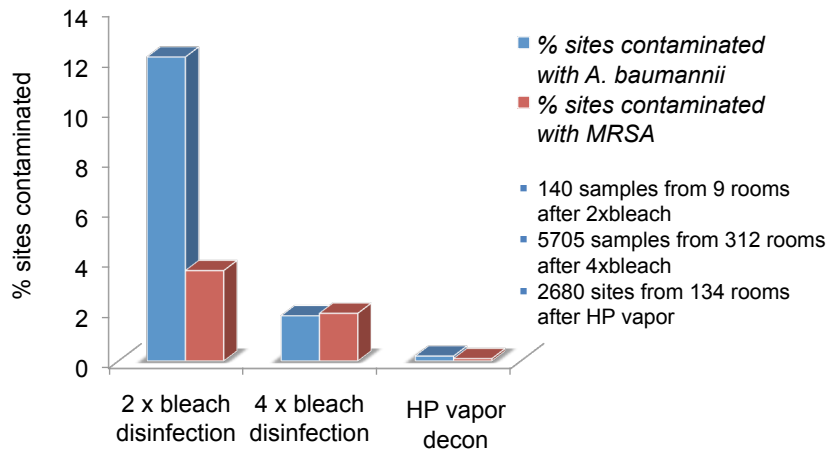
- *K. pneumoniae* seems to be more environmental than *E. coli*.^{1,2}
- Surface contamination on five standardized sites surrounding patients with ESBL-producing *Klebsiella* spp. (n=48) or ESBL-producing *E. coli* (n=46).¹



Risk factors for ESBL-E contamination = ESBL-KP, urinary catheter; carbapenem therapy was protective.³

1. Guet-Revillet et al. *Am J Infect Control* 2012;40:845-848.
 2. Gbaguidi-Haore. *Am J Infect Cont* 2013;41:664-665.
 3. Freeman et al. *Antimicrob Resist Infect Control* 2014;3:5.

Persistent contamination



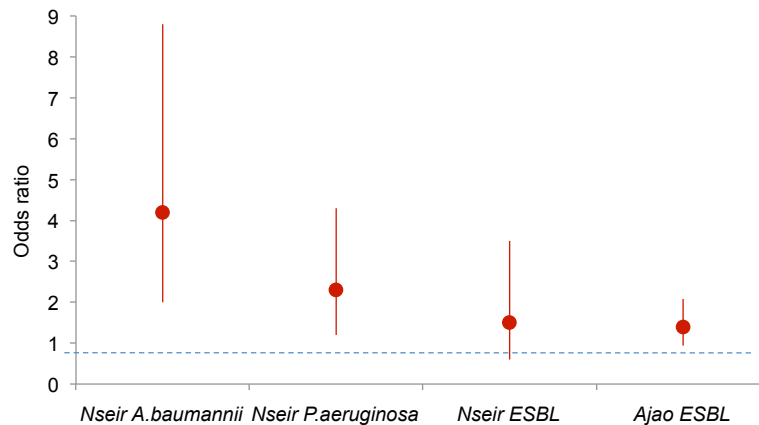
26.6% of rooms remained contaminated with either MRSA or *A. baumannii* following 4 rounds of bleach disinfection

Manian et al. *Infect Control Hosp Epidemiol* 2011;32:667-672.

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Enterobacteriaceae “less environmental”



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

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MDR-GNB cleaning & disinfection checklist

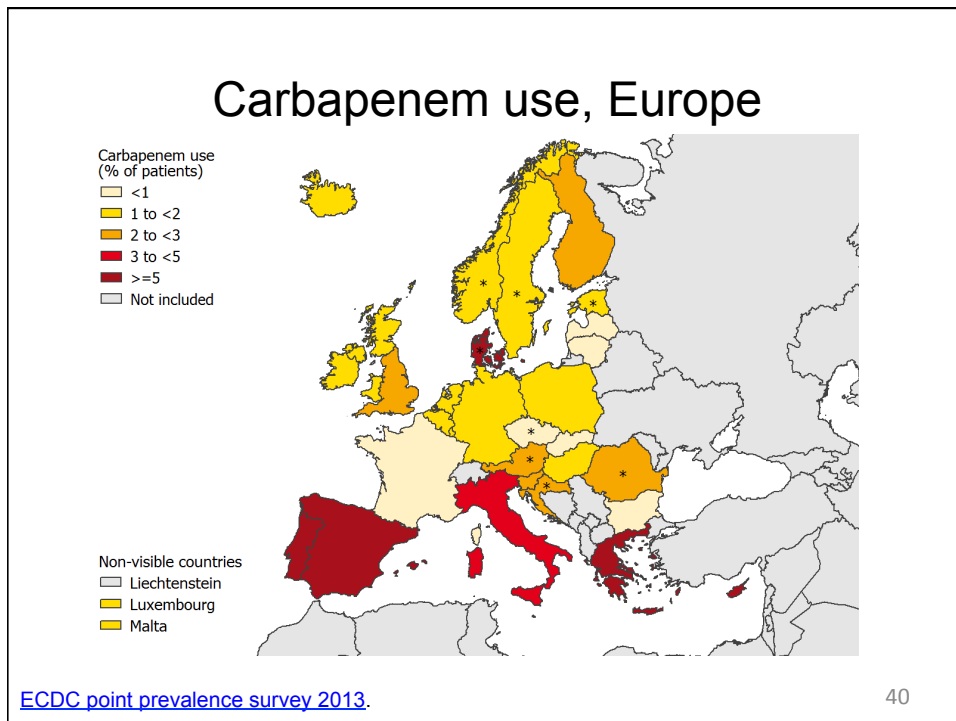
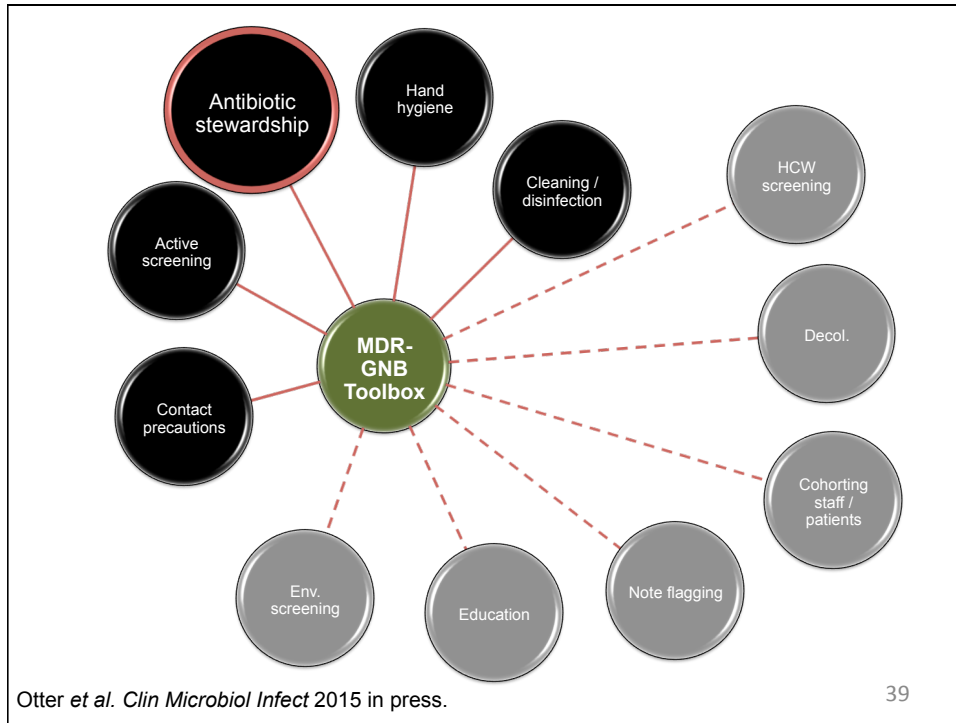
- Clean / declutter
- Monitor cleaning process (e.g. fluorescent markers)
- All equipment disinfected before leaving room
- Enhanced daily disinfection using bleach
- Terminal disinfection using bleach or, ideally, H₂O₂ vapor¹⁻³

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.

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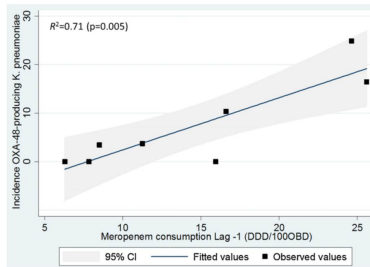
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Can we forecast a CPE storm?



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

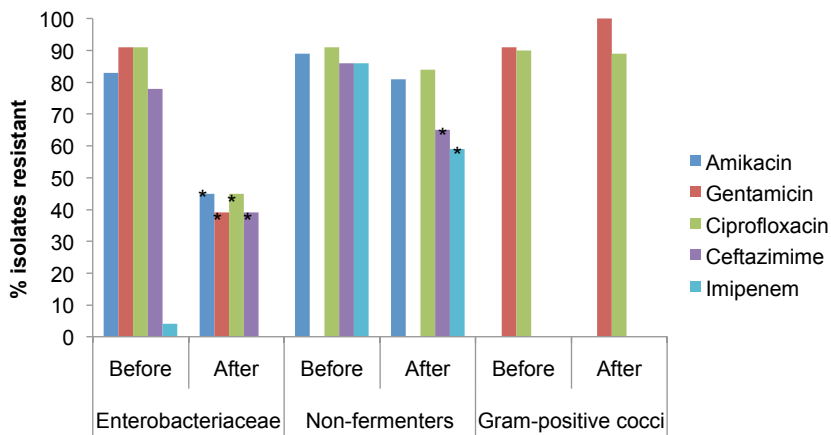
- Could we find and implement an “alert” level of carbapenem use?
- The authors claim a stewardship intervention brought the CPE outbreak under control – but also implemented ‘case isolation, screening of contacts, barrier nursing and other infection control interventions’.
- Study focussed only on OXA-48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

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

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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.

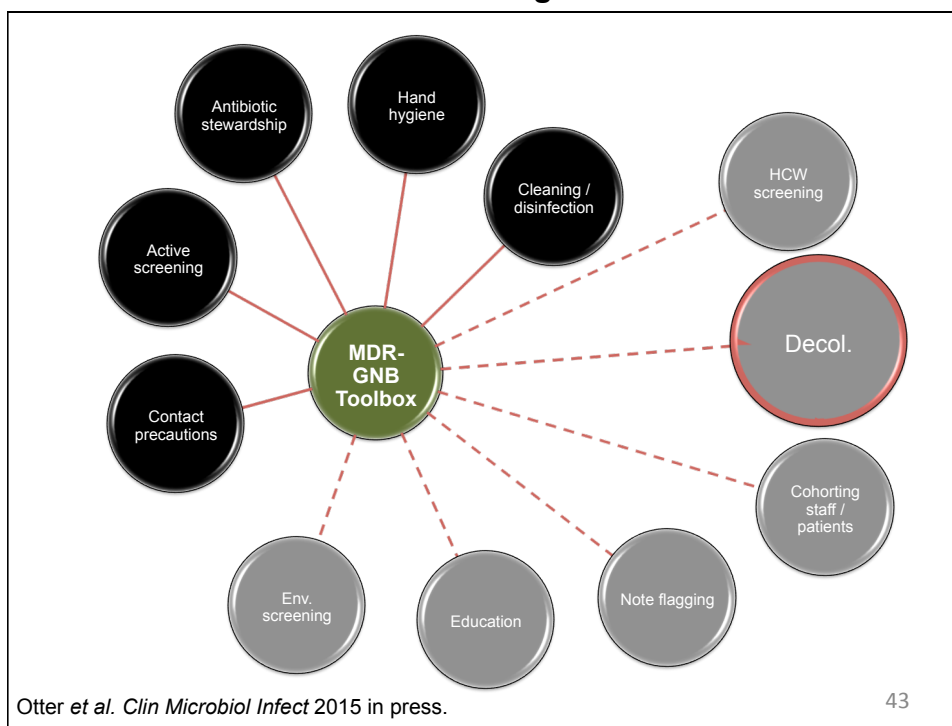


Hou et al. *PLoS ONE* 2014;9:e101447; * = significant difference before vs. after.

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Deisolation?

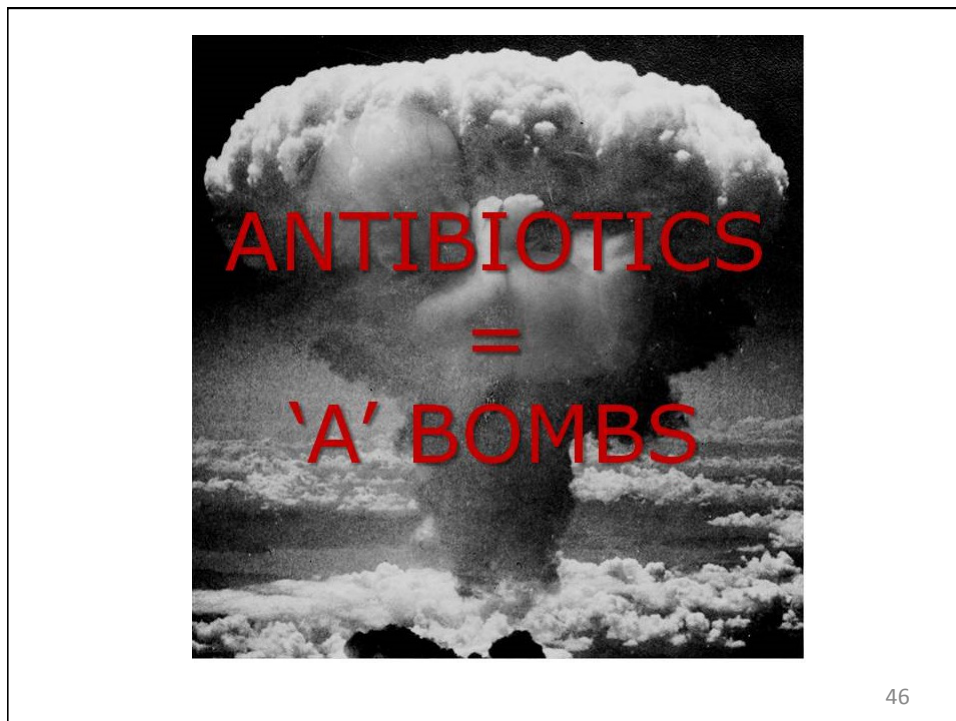
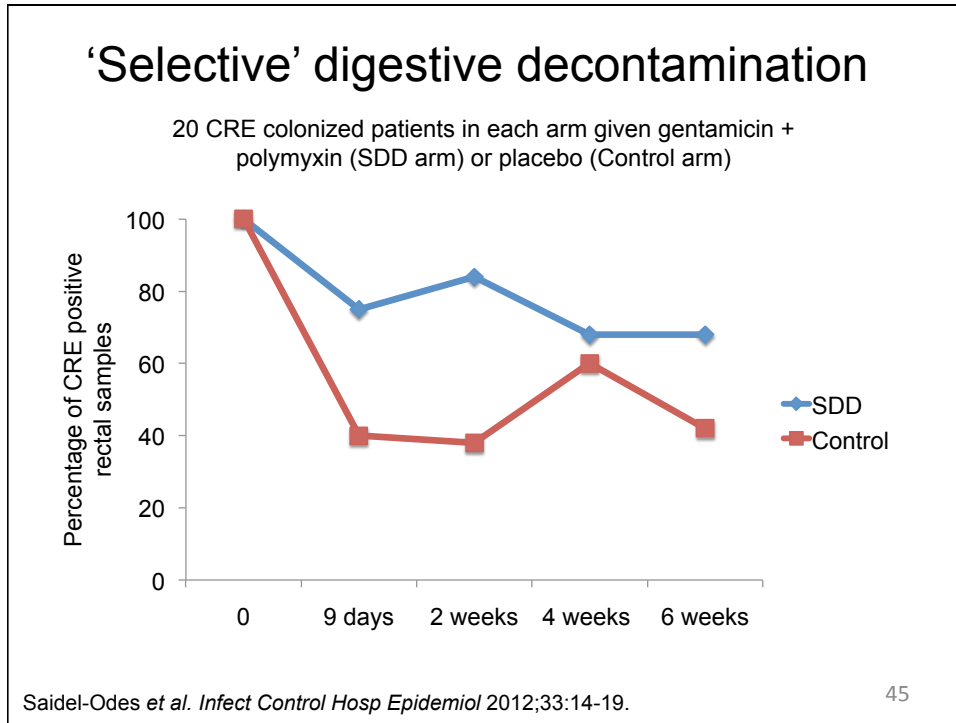
Author	Year	Setting	N pts	Organism	Duration of colonization
Bird ¹	1998	Elderly care facilities, Scotland	38	ESBL <i>K. pneumoniae</i>	Mean 160 days (range 7-548)
Pacio ²	2003	Long term care facility, USA	8	Resistant Gram-negative rods	Median 77 days (range 47-189)
Zahar ³	2010	Paediatric hospital, France	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.

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Decolonisation using faecal microbiota transplantation (FMT)

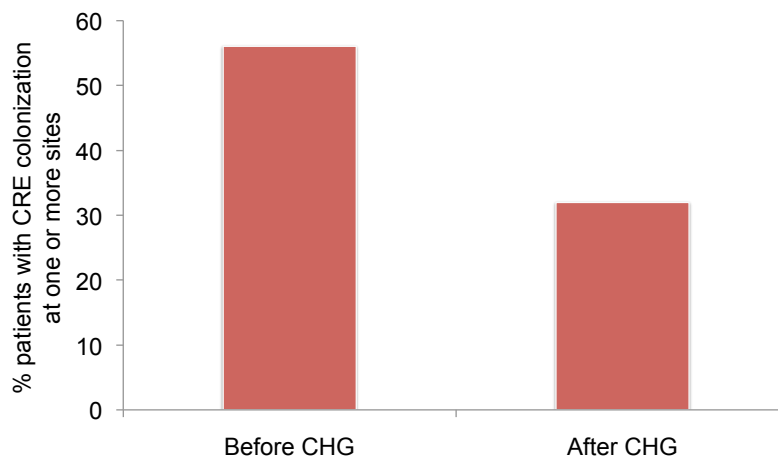
- 82 year old colonised with CPE.
- Carriage was delaying her admission to a nursing home.
- Single dose of FMT decolonised her at 7 and 14 days.

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

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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.

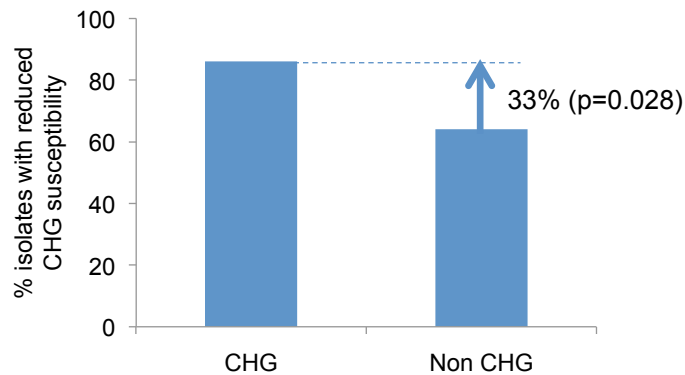
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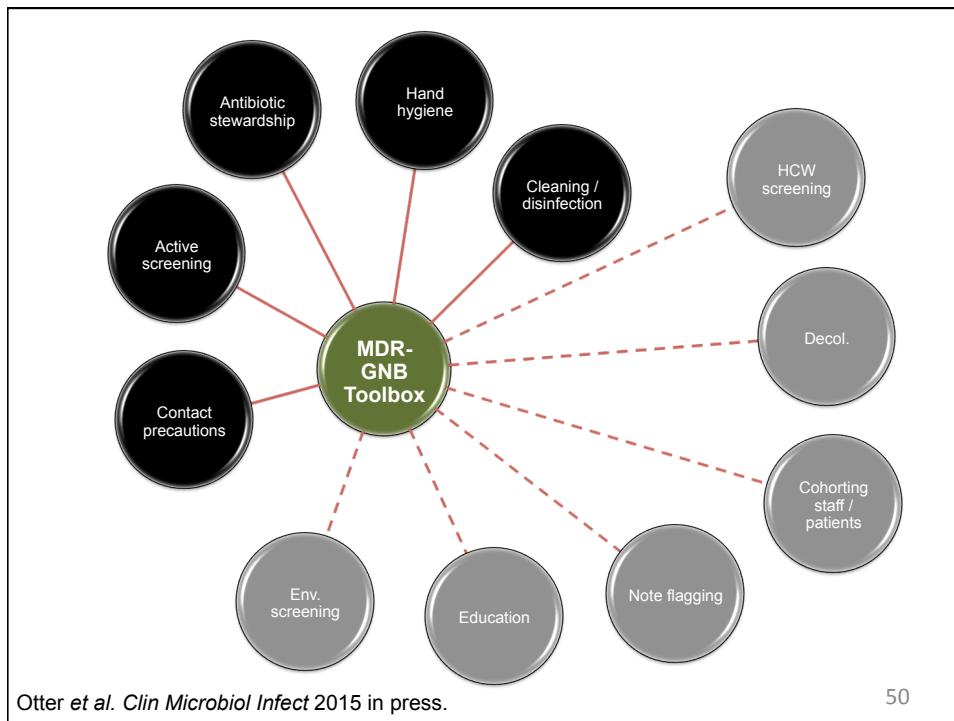
Chlorhexidine – reduced susceptibility

Proportion of BSI isolates with reduced susceptibility to chlorhexidine on units using chlorhexidine gluconate (CHG) daily bathing (n=28) or not (n=94).



Suwanarat et al. *Infect Control Hosp Epidemiol* 2014;35:1183-1186.

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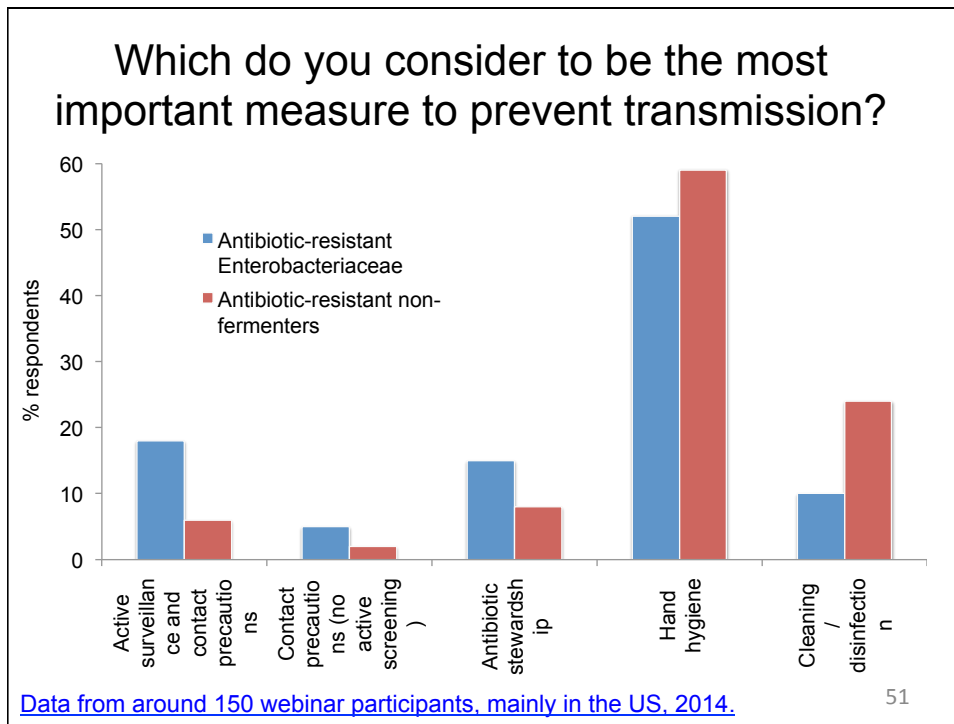


Otter et al. *Clin Microbiol Infect* 2015 in press.

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Rising to the Challenge of Multidrug-Resistant Gram-Negative Bacteria
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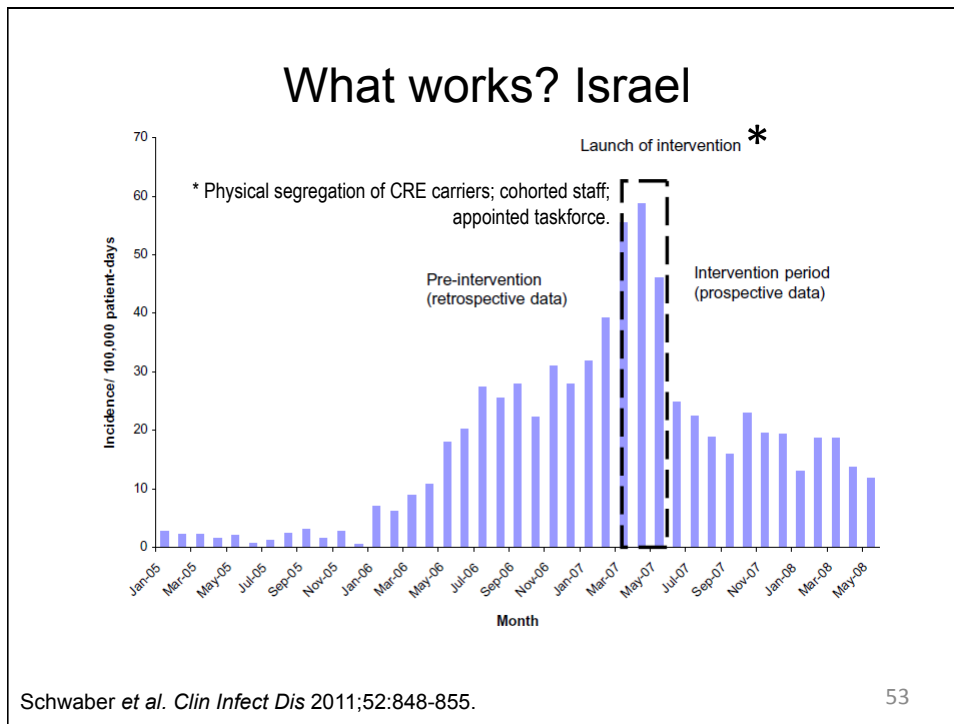


Type	n studies	Failure rate	Odds ratio
Bundled intervention	75	28%	1.9
Single intervention	11	45%	

Cataldo *et al.* ECCMID 2014. 0125.

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Key questions

- Which interventions work?
- Are they different for Enterobacteriaceae and non-fermenters? (Probably, given their epidemiology.)
- What is the prevalence of CPE?
- How much do we believe a single negative screen? What is the duration of colonisation?
- Do we need rapid molecular diagnostics?
- Are there decolonisation strategies other than (virtually non) 'selective decontamination' using abx?

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Summary

1. MDR-GNB are emerging worldwide and represent a unique threat.
2. CPE in particular combine resistance, virulence and the potential for rapid spread.
3. Prevalence in the US appears to be patchy, but increasing.
4. We do not yet know what is effective in terms of prevention and control, but screening and isolation of carriers seems prudent.
5. Diagnosis can be challenging, and relies on close liaison with the microbiology laboratory.

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