Public Health England

Protecting and improving the nation's health

Disinfectant use and antimicrobial resistance

Webinar – Promoting safer disinfectants in the global healthcare sector
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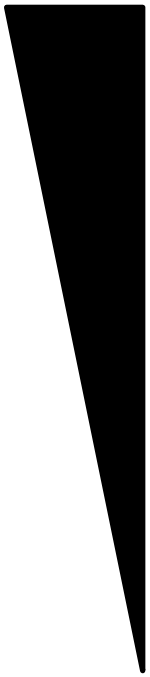
Antibiotics are failing which places even greater pressure on disinfectants/biocides and hospital disinfection policy

Prevention is better than cure

Classification of micro-organisms according to their resistance to biocides.

High Resistance



Prions (CJD, BSE)
Coccidia (*Crytosporidium* spp)
Bacterial endospores (*Bacillus* spp. *Clostridium difficile*)
Mycobacteria (*Mycobacterium tuberculosis, avium, terrae*)
Cysts (*Giardia*, *Taenia* spp)
Small non-enveloped viruses (Poliovirus)
Trophozoites (*Acanthamoeba* spp)
Gram-negative bacteria (*Pseudomonas* spp, *Escherichia coli*)
Fungi (including fungal spores) (*Aspergillus* spp, *Candida* spp)
Large non-enveloped viruses (Adenovirus)
Gram-positive bacteria (*Staphylococcus* spp, *Enterococcus* spp)
Large lipid enveloped viruses (HIV, HBV)

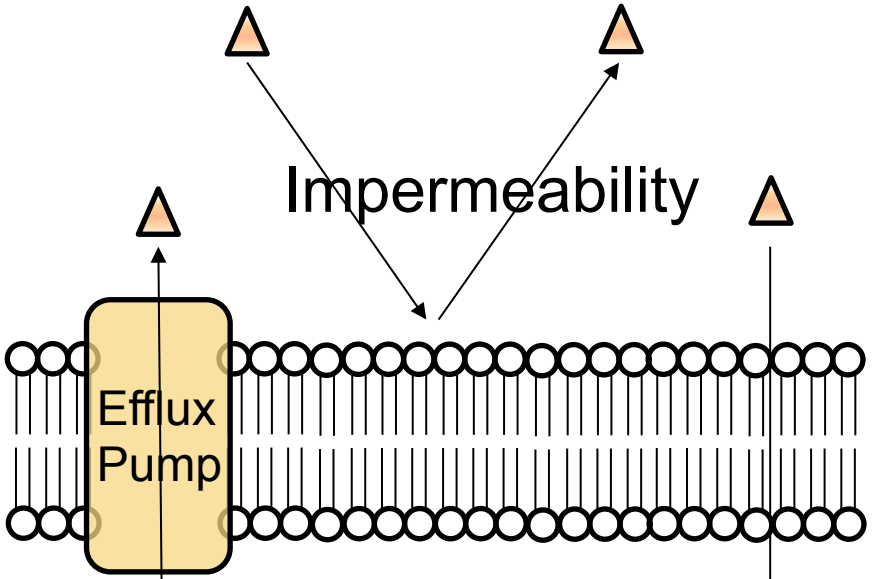
Low Resistance

Groups containing bacteria are highlighted in bold. Adapted from Maillard, 2002

Questions associated with biocide resistance

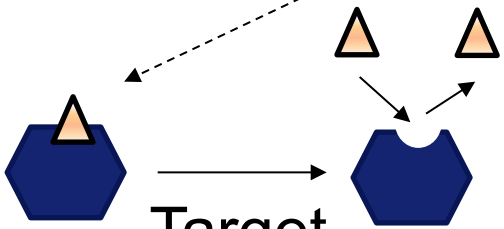
1) Why are we not seeing widespread resistance to biocides in hospitals such as is the case with antibiotics?
2) Have bacteria become more tolerant to biocides with constant exposure?
3) What are the resistance mechanisms (Phenotypic and Genotypic) to biocides in bacteria?
4) Is there a link between biocide resistance and antibiotic resistance?
5) Does the current level of biocide resistance matter?

General biocide resistance mechanisms



Change in Membrane Composition?

Enzymatic degradation



Target Modification

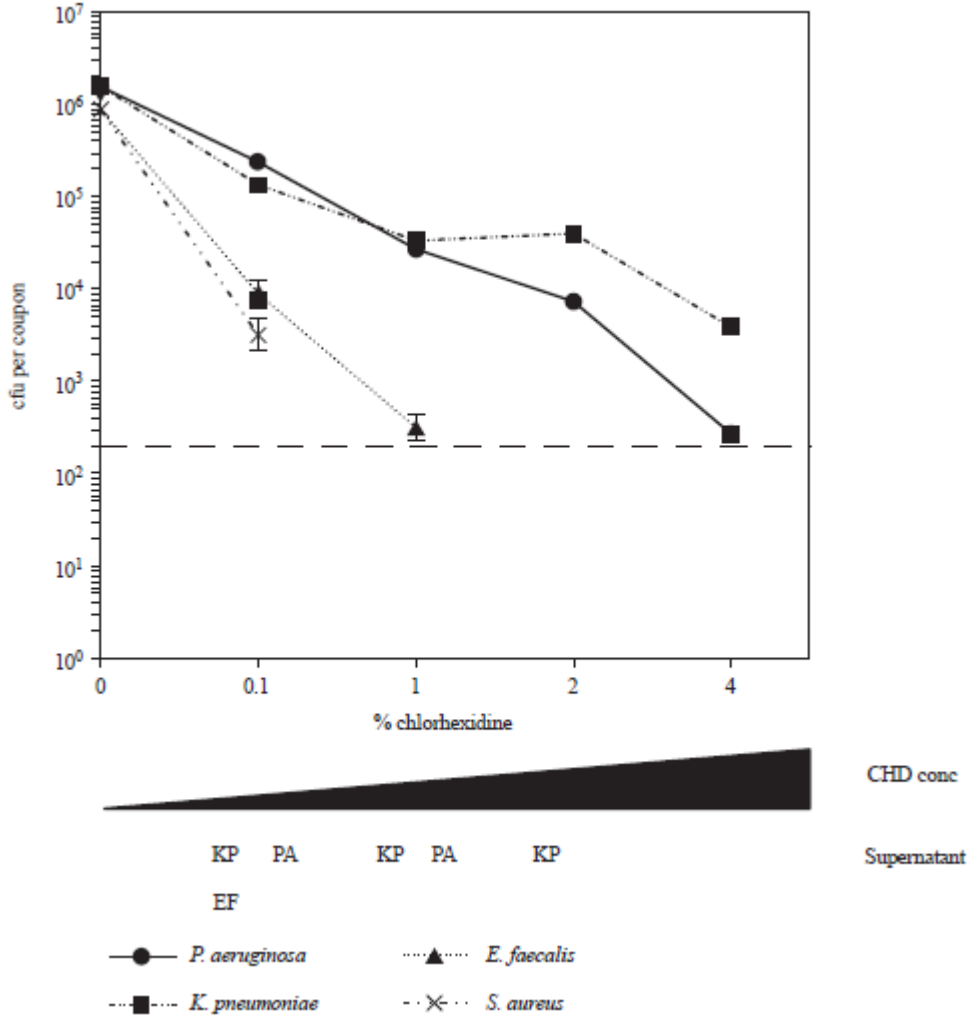
Planktonic to biofilm form bacteria – bacteria in biofilms are more resistant to biocides.

Chlorhexidine is less effective against Gram-negative biofilms

Table I
Chlorhexidine gluconate MIC/MBC/MBEC values (mg/L) for the four strains used in the mixed-species biofilm reactor

Organism	Strain	MIC	MBC	MBEC	Biofilm
Pseudomonas aeruginosa	PAO1	8	64	>512	+++
Klebsiella pneumoniae	NCTC 13368	16–32	32	>512	++
Enterococcus faecalis	NCTC 775	2	4	16	+++
Staphylococcus aureus	ATCC 9144	≤0.5	1	8	+

MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration; MBEC, minimum biofilm eradication concentration.

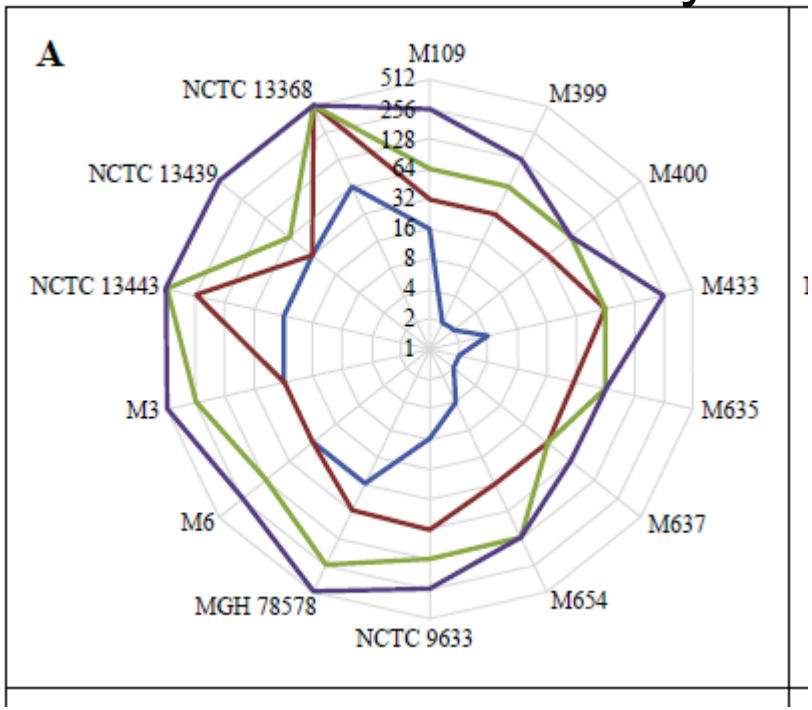


Touzel *et al*, 2016 *J. Hosp Infect* **92**:154-60

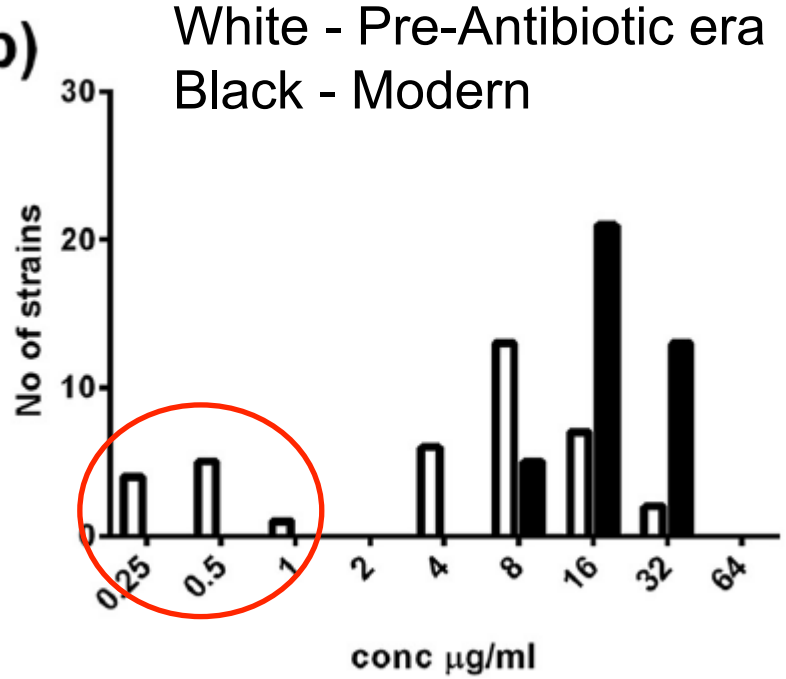
Klebsiella has become more tolerant to chlorhexidine over time.

Modern

Murray



Bock *et al*, 2016 *J. Hosp Infect* **93**:42-8



Wand *et al*, 2015 *Antimicrob Agents Chemother* **59**:3966-72

Adaptation to chlorhexidine leads to acquisition of colistin resistance

Strain	CHD	CHD + CCCP	BCl	Oct	HDPCM	EtOH (%)	CST	CST + CCCP	AZM	FEP	TEC
M109 WT	8	0.5-1	16	4	4-8	3.125	2	2	8-16	0.06-0.125	>64
M109 CA	32-64[a]	0.5-1	8-16	2-4	4-8	6.25	2-4	0.5-1	8-16	0.06-0.125	>64
NCTC 13439 WT	8-16	2-4	16	2-4	16	6.25	4	2	32	>64	>64
NCTC 13439 CA	256[a]	1-2	16	2-4	8-16	6.25	>64[a]	1	32	>64	>64
M3 WT	8-16	1-2	8-16	2-4	8	6.25	2-4	2	16-32	>64	>64
M3 CA	32-64[a]	0.5-2	8-16	2-4	8-16	3.125	>64[a]	1-2	8-16	>64	>64
NCTC 13443 WT	8-16	1-2	8-16	4	8-16	3.125	2	2	64	>64	>64
NCTC 13443 CA	256-512[a]	1-2	8-16	2	8-16	3.125	>64[a]	2	16-32	>64	>64
NCTC 13368 WT	32	2-4	32	4-8	32-64	6.25	2-4	2-4	64	64	>64
NCTC 13368 CA	256[a]	1-2	16	4-8	16	6.25	>64[a]	2-4	64	64	>64
MGH 78578 WT	8-16	1-2	8-16	4	8-16	6.25	2-4	2-4	32	>64	>64
MGH 78578 CA	256-512[a]	0.5-2	8-16	4	8	3.125	>64[a]	1-2	32-64	0.5[a]	>64

[a] ≥ 4-fold increase or decrease in MIC for chlorhexidine-adapted strains (CA) relative to non-adapted strains (WT)

Wand *et al*, 2017 *Antimicrob Agents Chemother* , e01162-16

Summary of Genotypic/Phenotypic attributes for chlorhexidine-adapted strains

	Mutations		Phenotype	
Strain	*phoP/Q*	*pmrK upregulation*	CST Res	Virulence
NCTC 13368	Y98C (PhoP)	18	Increased	Loss of virulence
MGH 78578	L348Q (PhoQ)	24	Increased	Loss of virulence
M109	No change	-	No change	Loss of virulence
NCTC 13439	No change	12	Increased	No loss of virulence
M3	E28K (PhoP)	64	Increased	No loss of virulence
NCTC 13443	A20P (PhoQ)	26	Increased	Loss of virulence

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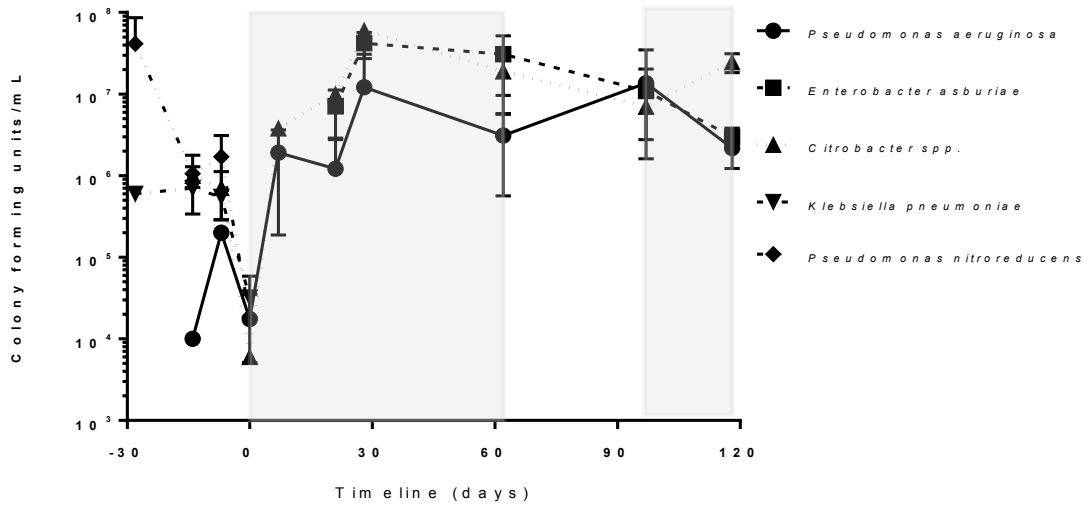
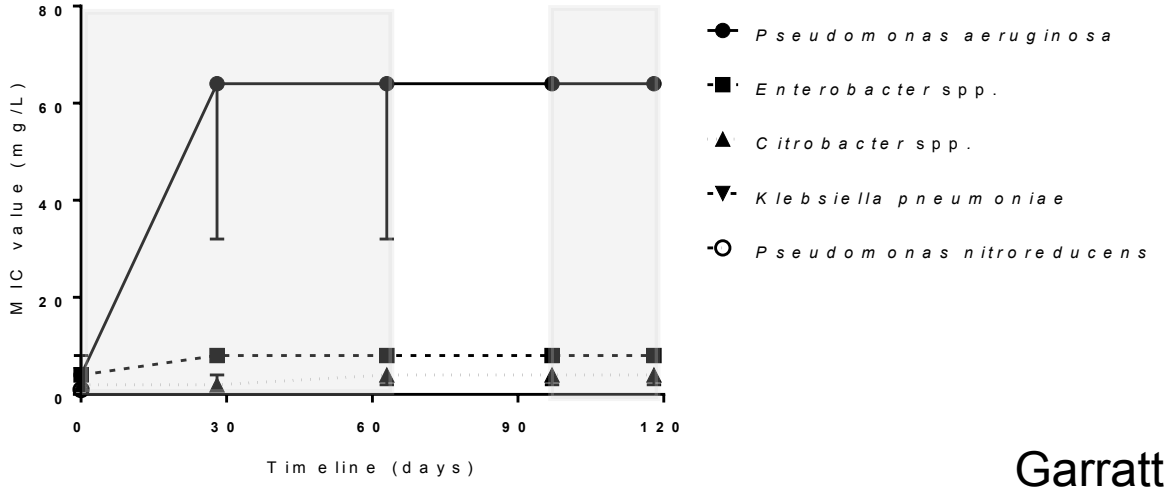
Effects on the Gram-negative population in a hospital sink trap after exposure to sub-lethal levels of octenidine





Garratt et al, 2020 submitted

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Organism	Increase in Octenidine Res	Biocide Cross-Resistance	Antibiotic Cross-Resistance	Growth	Virulence	Important Genes
P. aeruginosa	Yes (>4-fold)	No	No	WT	WT	*smvA* PA3458-PA3461
***Enterobacter* spp.**	Slight (2-fold)	Yes (multiple biocides)	Yes (ciprofloxacin)	WT	WT	*smvA* *malT* *ramR* *torA*
***Citrobacter* spp.**	Slight (2-fold)	No	Yes (Select β-Lactams, ciprofloxacin	Retardation	Loss of virulence	*marR* *ramR* *torS* *envZ*

MarR, RamR – regulators of the MDR efflux pump AcrAB-TolC

Conclusions

1) Organisms, in a biofilm, are more resistant to chlorhexidine, survival is above clinical concentrations
2) Modern clinical strains of *K. pneumoniae* appear to be more intrinsically resistant to chlorhexidine (Murray verses Modern strains)
3) Adaptation to chlorhexidine selects for cross-resistance to colistin through overexpression of *pmrK*
4) Exposure to continuous sub-lethal levels of disinfectant selects for particular species
5) Certain strains have increased resistance to antibiotics through mutations in efflux pump regulators.

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