The impact of disinfectants on antimicrobial resistance

An Ayliffe prediction

Prof Shaheen Mehtar
Infection Control Africa Network
smehtar@sun.ac.za

Infection Control Africa Network   www.webbertraining.com   October 2, 2018

Disclosures

Copper Development Association Africa: research funds for Masters project:

- "Viability of TB after re-aerosolization and the effect of copper"
- "Water containers for household in endemic cholera areas"

Biomerieux: consultant for Global PPS programme- Africa (2018)

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Prof G Ayliffe- Predictions

..."Aseptic methods are often poor, the use of disinfectants was excessive and inadequately controlled and defects in sterilization were common (Forward: *Ayliffe's* Control of Healthcare Associated Infection, 2009)

..."however alternatives are sometimes necessary due to the lack of resources such as clean water, electricity & disposables" (Forward: Hospital Infection Control, Setting up a cost effective programme, 1992)

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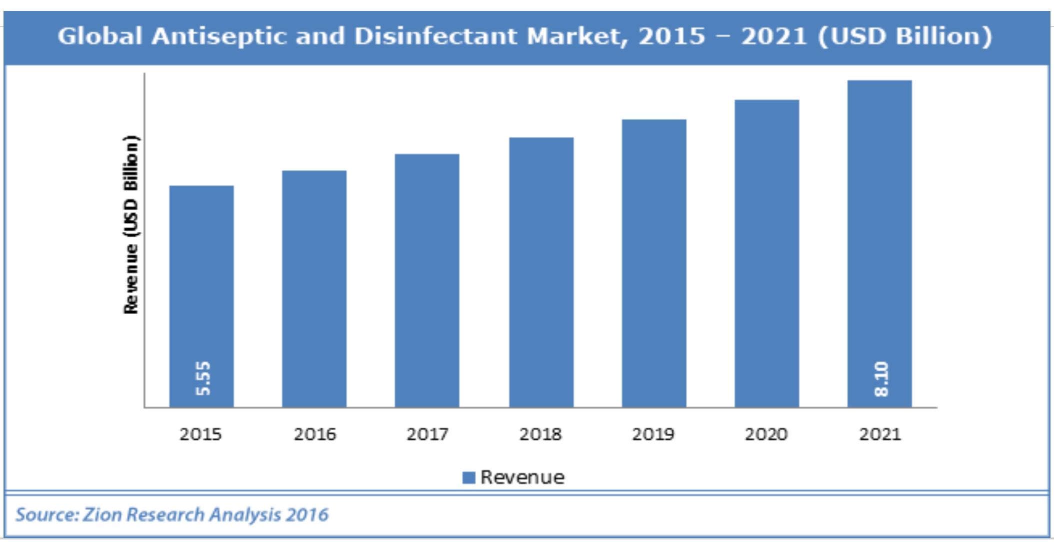
Global Market 2015



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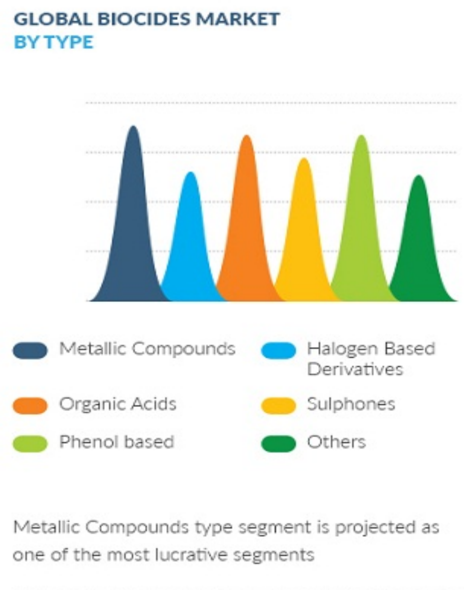
Classes of disinfectants & sanitizers

- ✓ Iodophors,
- ✓ quaternary ammonium compounds (QAC),
- ✓ peroxides,
- ✓ phenols,
- ✓ chlorine,
- ✓ glutaraldehyde



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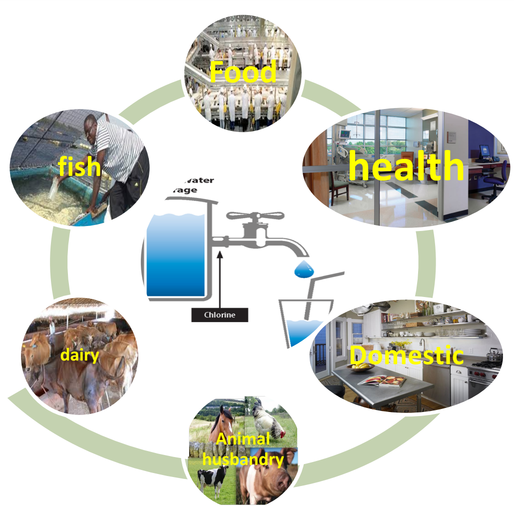
Use of disinfectants



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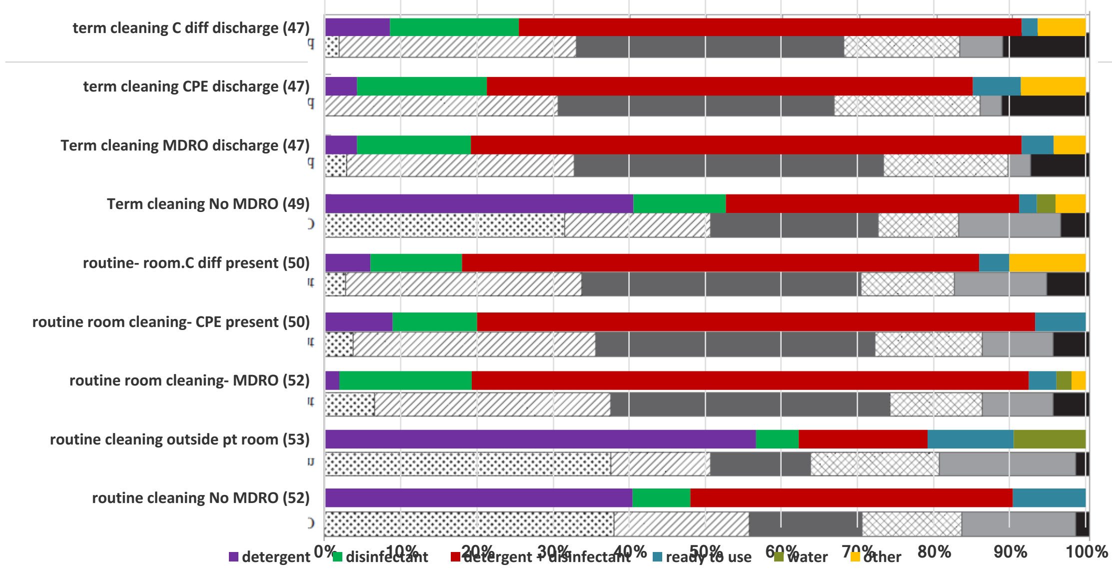
survey on cleaning & disinfection



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International Survey of cleaning & disinfection practice in the healthcare environment. Venter N, et al. JHI. 2018

France

Journal of Hospital Infection 97 (2017) 226–233

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Incidence, risk factors, and outcome of multidrug-resistant *Acinetobacter baumannii* acquisition during an outbreak in a burns unit☆

A.-L. Munier[a,*], L. Biard[b], C. Rousseau[c,†], M. Legrand[d,e,†], M. Lafaurie[a], A. Lomont[c], J.-L. Donay[c], E. de Beaugrenier[f], R. Flicoteaux[b], A. Mebazaa[d], M. Mimoun[g], J.-M. Molina[a]

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Findings

Prospective study Burns Unit, Paris- April- Nov 2014

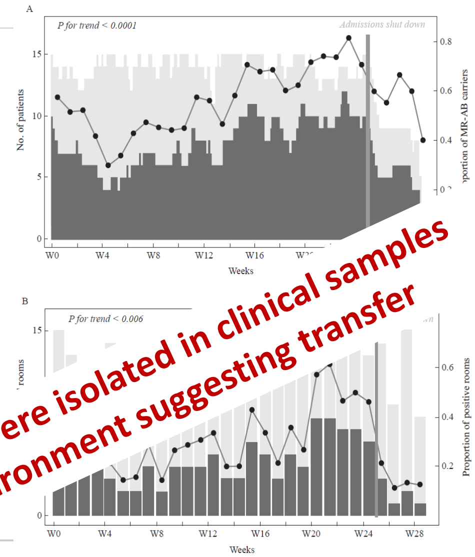
Screening at admission & weekly from patients and environment

25/ 86 (32%) patients acquired MR-AB; 9 pre-colonised (total= 34)

Room environment colonization in 25/34 (74%).

multi locus sequence typing : MR-AB (ST2) found in 94% patients and 92% environmental strains, all had blaOXA-23 gene.

Of the 25 patients acquiring MR-AB colonization during hospitalization, MR-AB strains were isolated in clinical samples *before* the environment in 15/25 (60%) patients.



lumber and proportion of multidrug-resistant *Acinetobacter baumannii* (MR-AB)-positive patients (A) and MR-

MR-AB strains were isolated in clinical samples before the environment suggesting transfer

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Acinetobacter susceptibility to abt & disinfectants

- 238 clinical isolates of Acinetobacter spp tested against chlorhexidine gluconate, benzethonium chloride, gentamicin, amikacin, acriflavine, tetracycline and ethidium bromide, alkyldiaminoethylglycine hydrochloride (10% w/v), ceftazidime, imipenem,and ciprofloxacin
- Significant differences (P,0.01) were observed between disinfectant-susceptible and DRS isolates in the time–kill assays of chlorhexidine gluconate, benzalkonium chloride and benzethonium chloride.
- DRS isolates tended to demonstrate multi resistance profiles to ceftazidime, ciprofloxacin and amikacin (P,0.05).

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J Antimicrob Chemother 2010; **65**: 1975–1983

Acinetobacter susceptibility to abt & disinfectants

Table 3. Correlation between MICs of disinfectants and antimicrobial agents

Antimicrobial agent	Category[a]	Number of strains	Median MIC (mg/L)	Spearman's correlation coefficient (*P* value) CHX	BZK	BZT	ADH
CAZ	S	247	4	0.336 ($P<0.01$)	0.300 ($P<0.01$)	0.193 ($P<0.01$)	0.292 ($P<0.01$)
	I	13	16				
	R	23	64				
IPM	S	268	0.5	0.095 ($P=0.114$)	0.130 ($P<0.05$)	0.035 ($P=0.559$)	0.008 ($P=0.900$)
	I	2	8				
	R	13	32				
CIP	S	252	0.25	0.224 ($P<0.01$)	0.319 ($P<0.01$)	0.128 ($P<0.05$)	0.287 ($P<0.01$)
	I	4	2				
	R	27	32				
AMK	S	268	2	0.189 ($P<0.01$)	0.193 ($P<0.01$)	0.142 ($P<0.05$)	0.223 ($P<0.01$)
	I	4	32				
	R	11	64				

CHX, chlorhexidine gluconate; BZK, benzalkonium chloride; BZT, benzethonium chloride; ADH, alkyldiaminoethylglycine hydrochloride; CAZ, ceftazidime; IPM, imipenem; CIP, ciprofloxacin; AMK, amikacin.
[a]Susceptibilities of 283 isolates of *Acinetobacter* spp. to CAZ, IPM, CIP and AMK were categorized into susceptible (S), intermediate (I) and resistant (R) in accordance with CLSI criteria.

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J Antimicrob Chemother 2010; **65**: 1975–1983

Chlorhexidine, *K pneumoniae* & colistin

- Adaptation to chlorhexidine resistance led to colistin resistance in 5 of 6 strains of *K pneumoniae*.
- Mechanism: mutation of regulator genes (*smvR*) next to MFS regulatory efflux pump *smvA* gene
- **The *phoPQ* (from CHG adapted strain) insertion into *K pneumoniae* resulted in colistin resistance but not chlorhexidine resistance.**

TABLE 3 MIC and MBC values of CHD and CST after plasmid complementation[a]

Strain	Plasmid	Description	CHD MIC (mg/liter)	CHD MBC (mg/liter)	CST MIC (mg/liter)	CST MBC (mg/liter)
M109 CA	pACYC-184 alone	Empty vector	32	32	2–4	2–4
	pACYC M3 *smvR* WT	*smvR* from strain M3	8	8	2	2
	pACYC M3 *smvR* CHD	*smvR* from strain M3 CA	32	32	2–4	2–4
	pACYC 13443 *smvR* WT	*smvR* from strain NCTC 13443	8	8	2	2
	pACYC 13443 *smvR* CHD	*smvR* from strain NCTC 13443 CA	32	32	2–4	2–4
	pACYC *phoPQ* WT	*phoPQ* from strain NCTC 13443	32–64	32–64	1–2	2
	pACYC *phoQ* A20P	*phoPQ* from strain NCTC 13443 CA	32–64	64	64	64–>64
M109 WT	pACYC-184 alone	Empty vector	8–16	8–16	0.5–1	2–4
	pACYC *phoPQ* WT	*phoPQ* from strain NCTC 13443	8–16	8–32	0.5–1	2–4
	pACYC *phoQ* A20P	*phoPQ* from strain NCTC 13443 CA	8–16	16–32	32–64	64
25	pACYC-184 alone	Empty vector	8–16	8–16	0.5	2–4
	pACYC *phoPQ* WT	*phoPQ* from strain NCTC 13443	8–16	16–32	0.5–1	1–4
	pACYC *phoQ* A20P	*phoPQ* from strain NCTC 13443 CA	8–16	16–64	32–64	32–>64

[a]Levels of resistance to CHD and CST were measured after electroporation of the plasmids into the strains listed. All the MICs are shown as ranges of the results of at least three independent experiments.

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Antimicrob Agents Chemother 61:e01162-16.
https://doi.org/10.1128/AAC.01162-16.

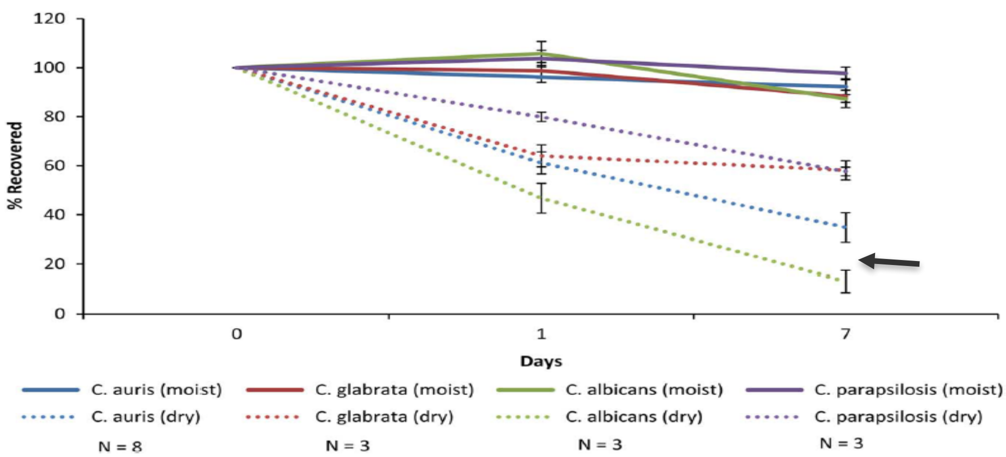
C auris- the new kid on the block

Environmental Surfaces in Healthcare Facilities are a Potential Source for Transmission of *Candida auris* and Other *Candida* Species

Christina T. Piedrahita, BS;[1] Jennifer L. Cadnum, BS;[1] Annette L. Jencson, CIC;[1] Aaron A. Shaikh, BS;[2] Mahmoud A. Ghannoum, PhD, FIDSA;[3,4] Curtis J. Donskey, MD[2,5]

Infect Control Hosp Epidemiol 2017;38:1107–1109

Recovery rates of *C auris* from environment (lab)



Recovery rates of *C. auris* at 1d and 7d > *C. albicans* but < *C. parapsilosis* (P< 05).

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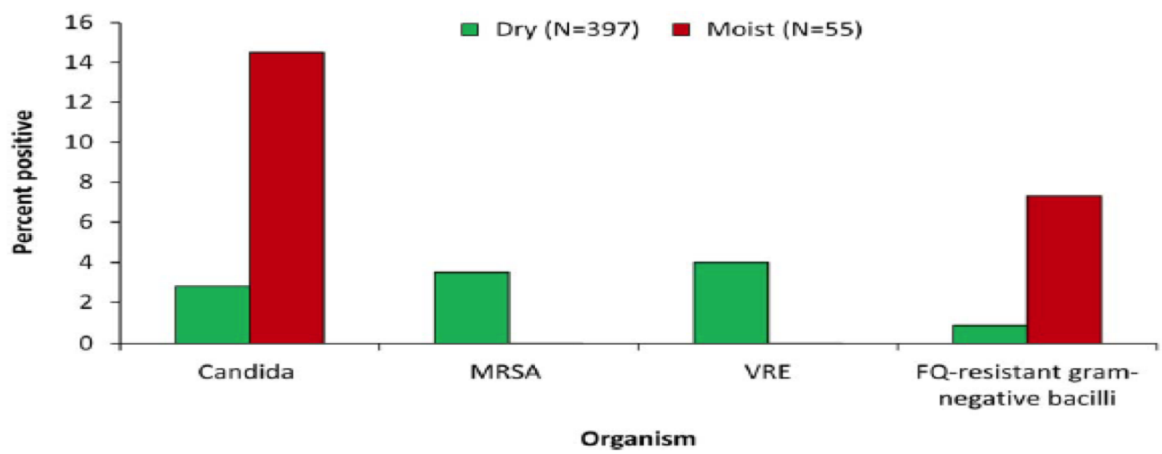
Survival of *C auris* on surfaces in HCF (clinical)



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Sinks and hand wash basins!

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Spain

Journal of Hospital Infection xxx (2017) 1–7

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

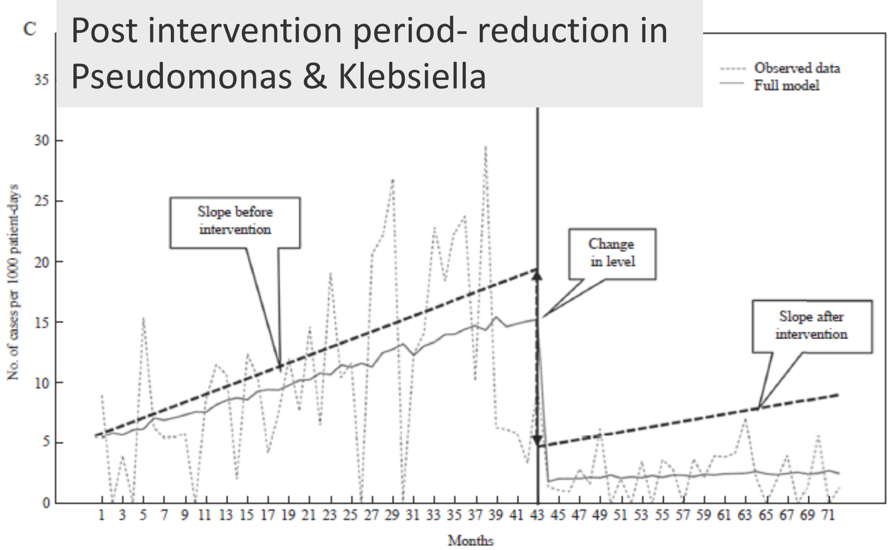
ELSEVIER

Control of endemic multidrug-resistant Gram-negative bacteria after removal of sinks and implementing a new water-safe policy in an intensive care unit

E. Shaw[a,b,*], L. Gavaldà[c], J. Càmara[d], R. Gasull[e], S. Gallego[e], F. Tubau[d,f], R.M. Granada[e], P. Ciercoles[a], M.A. Dominguez[d,b,g], R. Mañez[e], J. Carratalà[a,b,g], M. Pujol[a,b]

Crude rates reduction of MDRO

Post intervention period- reduction in Pseudomonas & Klebsiella



Biofilm

- Challenge in food industry, home and healthcare
- Within the biofilm
  - Cells within an exopolymeric matrix out-survive those on the surface of the biofilm
  - Repeated chronic exposure to sub-lethal treatments select for a resistant population that share this resistance with other microbes.
  - gene *SigB* is activated in both static and continuous biofilm production in wild strains and is involved in planktonic cells and biofilm- **resistance to peracetic acid & benzalkalonium chloride**
  - The biocide concentration is strongly affected by the reduced diffusion of active molecules through the biofilm (A(nderson and O'Toole 2008, Lewis 2008, Maillard 2007, Tart and Wozniak 2008).

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App Env Micro, 2010

Selection pressure - AWD

- Exposure to benzalkonium chloride (a QAC) showed a population shift and a selection of *Pseudomonas spp* following treatment.
- Emergence of 2% glutaraldehyde resistant *Mycobacterium chelonae*
- Gram positive bacteria isolated from AWD following a high level disinfection process using chlorine dioxide.
- The low concentration of the disinfectant or the presence of biofilms (Babb 1993, Pajkos et al. 2004, Smith and Hunter 2008), determine the reduced susceptibility to biocides

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Griffiths et al. 1997, Kingeren and Pullen 1993, Nomura et al. 2004

Triclosan

Uses: household products- toothpaste, soap, lotions

Resistance reported

- ***S aureus*****-** cross resistance with mupirocin- ***mup* gene**
- *E. coli. ARC ab* **flux pumps-** active transport of disinfectants and antibiotics. MDR
- **Pseudomonas spp**: expression of the *MexAB-OprM* **efflux system**. Selected high frequency MDR. cip^r
- **Acinetobacter spp- efflux pumps**
- ***M smegmatis*****:** ***Fab1* gene** insusceptibility to triclosan and isoniazid and vice versa
- ***Proteus mirabilis*** emerging triclosan resistance

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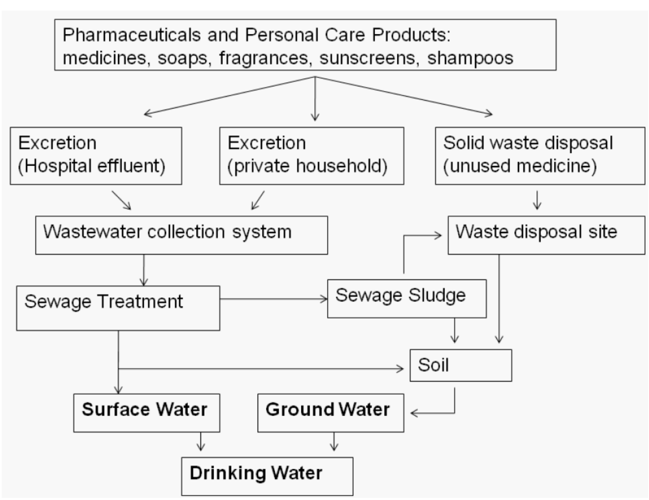
AAC Feb 2001; 45:

How much disinfectants are found in waterways



- 84% of antimicrobial bar soaps contain Triclocarban using as high as 750 metric tonnes/year (USA)
- Triclosan in 57% of the 139 waterways tested nationwide (USA).
- High levels found in effluent from hospitals and waterways.
- Primary biodegradation in aerobic soil gave a half-life for triclosan of 18 days!
- In the presence of hypochlorite or sunlight converts to dioxins and other toxic compounds
- Absorbed in human (mothers milk) and aquatic life (rainbow trout),
- Sweden abandoned triclosan use in hospitals

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PhD thesis 2012. M Alshuli, Phil.USA

MRSA

- mupirocin resistance in MRSA strains carried a **quaternary ammonium resistance** gene (*qacA*) located in a gentamicin resistance plasmid that encoded for an efflux mechanism resulting in low-level chlorhexidine resistance.
- **Transferable triclosan** resistance in MRSA has been described, occurring together with a high-level of mupirocin in a hospital environment

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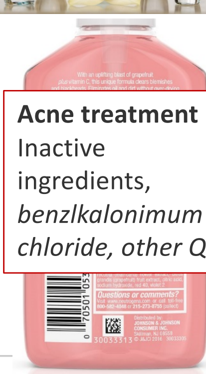
Quaternary Ammonium compounds (QAC)

Uses: household, cosmetics, perfume

- 238 Clinical b/c isolates of *S aureus* and *S epidermidis* from children
- In 78 BC^r staphylococcal isolates, resistance to QAC- 50%
- **plasmids**- *qacA* or*B* (*qacA/B*), *qacC*, *blaZ*, and *tetK*
- *Qac* linkage between disinfectants and penicillins in clinical isolates in Norway



Acne treatment
Inactive ingredients, *benzlkalonimum chloride, other QAC*

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Antimicrob. Agents Chemother. 2002 vol. 46 no. 92797-2

Mechanisms of resistance to biocides

Table 8 Bacterial mechanisms of resistance to biocides

Mechanisms	Nature	Level of susceptibility to other biocides[1]	Cross-resistance
Permeability	intrinsic (acquired)	no	yes
Efflux	intrinsic/acquired	reduced	yes
Degradation	acquired/intrinsic	reduced	no
Mutation (target site)	acquired	reduced	no[2]
Phenotypic change	Following exposure	reduced	yes
Induction (stress response)	Following exposure	variable	yes

[1] to other biocides - level of susceptibility defined according to the concentration of biocides

[2] not to other biocide, but cross-resistance with specific antibiotics

The induction of bacterial resistance has been described in almost all biocides, such as quaternary ammonium compounds, bisbiguanides and phenolics, as well as glutaraldehyde.

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Regulations adopted 2009

Directorate-General for Health & Consumers

Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

Assessment of the Antibiotic Resistance Effects of Biocides

Scientific Committees

Measuring resistance

Table 7 Methodologies to measure bacterial resistance

Methodology	Measuring	
	Resistance to a biocide	Change in phenotypes
MBCs	Yes	Yes
Bactericidal activity	Yes	Yes
Inactivation kinetic	Yes	Yes
MICs	No*	Yes
Growth kinetic	No	Yes

* An increase in MIC might provide information about a trend towards insusceptibility

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Contamination of disinfectants (HCF)

- *Ps aeruginosa* from iodophors- failed manufacturing
- *Serratia marcescens* from contaminated QAC & CHG
- *Burkholderia cepacia* from multi use disinfectants
- *Ps aeruginosa* resistance to metal such as silver- silver nitrate dressings
- *Ps aeruginosa* isolated from cosmetics and several other types of products is pathogenic and resistant to several types of antibiotics (Scully et al. 1986).

Chlorine & antimicrobial resistance

22 genera were isolated from chlorinated drinking-water with a range of susceptibilities to chlorine and antibiotics.

•Chlorine-resistant bacteria had higher MICs for tetracycline, sulfamethoxazole and amoxicillin.

• In the presence of free chlorine, antibiotic-sensitive bacteria survival was less than antibiotic-resistant bacteria.

Weak correlations were found between chlorine-tolerance and minimum inhibitory concentrations against the antibiotics tetracycline, sulfamethoxazole and amoxicillin (transmissible genes) but not against ciprofloxacin (efflux pumps and porins) so most likely not on the *mac* operon.

Antibiotic-resistant bacteria survived longer than antibiotic-sensitive organisms when exposed to free chlorine in a contact-time assay.

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Chemosphere, 2016: 152

Deliberate exposure to chlorine spraying- Ebola

Table 2 Chlorine spraying in the three groups

Site	HCW		EVD		NEVD	
Total interviewed	500		550		500	
Not sprayed (excluded)	7		0		23	
Total analysed	*N* = 493	%	*N* = 550	%	*N* = 477	%
In own house (under quarantine)	9	2	0	-	440 0	92
Outside in the community	0	-	0	-	21	4
Pre transfer	0	-	162	30	15	3
Back of ambulance	61	12	547	99	38	8·0
Leaving ETU			550	100		
Red zone	455	93	120	22		
Spray others	113	23				
In room when spraying others	116	24				
EVD case house	16	3				
EVD suspect house	33	7				

HCW = healthcare workers; *EVD* = Ebola virus disease survivors; *NEVD* = non Ebola cases

Table 5 Adverse events in HCW with single and multiple chlorine exposure compared

Characteristic	Single Cl_2 exposure (*N* = 285) n(%),	Multiple Cl_2 exposure (*N* = 208) n(%)	*P*-value
Eye sight problem before	19 (7)	25 (12)	0.04
Eye sight problem now	95 (34)	123 (59)	<0·001
Coughing	107 (38)	124 (60)	0·001
Cough producing sputum	43 (15)	60 (29)	<0·001
Difficulty in breathing	66 (23)	100 (48)	<0·001
Chest tightness	109 (38)	131 (63)	<0·001
Burning throat	85 (30)	112 (54)	<0·001
Skin irritation	95 (34)	109 (52)	<0·001

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Mehtar *et al. Antimicrobial Resistance and Infection Control* (2016) 5:45
DOI 10.1186/s13756-016-0144-1

American Journal of Infection Control 45 (2017) 1133-8
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journal homepage: www.ajicjournal.org
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AJIC American Journal of Infection Control

Major Article **163 staff interviewed; 49 air samples taken**

Health problems and disinfectant product exposure among staff at a large multispecialty hospital

CrossMark

Symptoms and self-reported diagnoses of the survey participants, by disinfectant product use at a hospital, August 2015

Health effect	All participants (N = 163)	Work-related symptoms*	Disinfectant product use (n = 78)	No disinfectant product use (n = 85)	P value†
Symptom					
Nasal problems‡	68 (42)	29 (18)	31 (40)	37 (44)	.64
Watery eyes‡	65 (40)	31 (18)	35 (45)	30 (35)	.26
Asthma-like symptoms§	46 (28)	16 (10)	24 (31)	22 (26)	.60
Skin problems‡	31 (19)	19 (11)	12 (15)	19 (22)	.32
Wheeze‡	26 (16)	6 (4)	12 (15)	14 (16)	>.99
Shortness of breath	21 (13)	7 (4)	11 (14)	10 (12)	.82
Chest tightness‡	18 (11)	4 (2)	10 (13)	8 (9)	.62
Cough	9 (6)	4 (2)	5 (6)	4 (5)	.74
Asthma attack‡	8 (5)	4 (2)	3 (4)	5 (6)	.72
Medication use					
Allergy medicine	48 (29)	9 (6)	16 (21)	32 (38)	<.05
Asthma medicine	18 (11)	6 (4)	10 (13)	8 (9)	.62

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EVS health

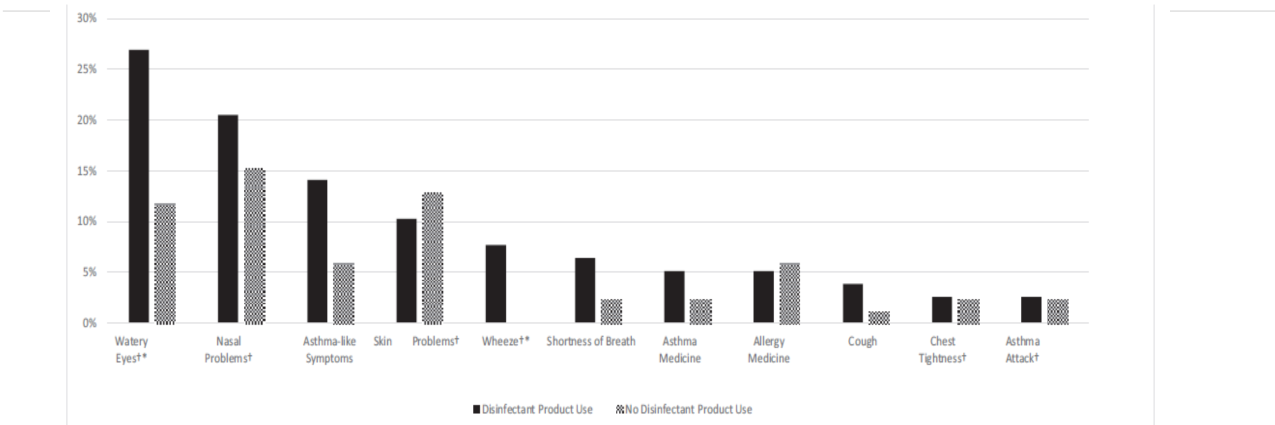

Fig 1. Prevalence of work-related symptoms by disinfectant product use at a hospital, August 2015. Work-related symptoms were defined as symptoms that improved away from the facility, either on days off or on vacation. *Statistically significant differences using χ^2 test ($P < .05$). †All symptoms specific to the last 12 months.

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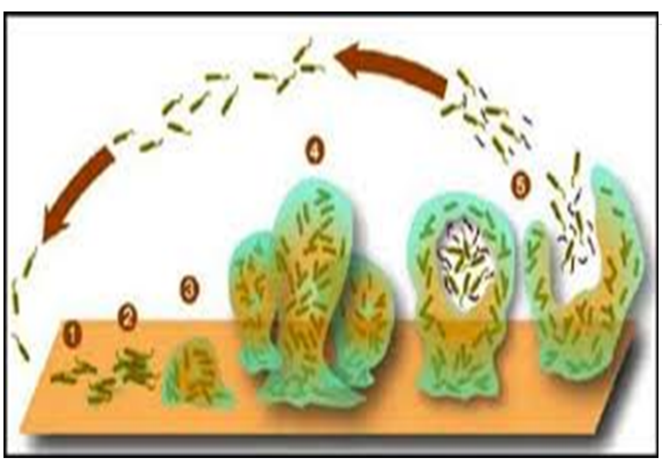
Take home message



It all boils down to removing the biofilm!

Disinfectants

- ✓ Sub-lethal doses
- ✓ Inadequate removal
- ✓ Inappropriate use

↓

Antimicrobial resistance

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Prof Ayliffe- A mentor to many

Prof Graham Ayliffe
1926- 2017
A gentleman and a scholar
who taught me to think!

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www.webbertraining.com/schedulep1.php

October 11, 2018	*(FREE CBIC Teleclass)* **INFECTION CONTROL CHAMPIONS ARE MADE, NOT BORN** Speaker: **To be announced**
October 17, 2018	*(South Pacific Teleclass)* **BIOFILMS IN THE HOSPITAL ENVIRONMENT - INFECTION CONTROL IMPLICATIONS** Speaker: **Prof. Karen Vickery**, Macquarie University, Australia
October 18, 2018	**INFECTION PREVENTION CORE PRACTICES: RESETTING THE BAR FOR SAFE PATIENT CARE** Speaker: **Prof. Ruth Carrico**, University of Louisville **Sponsored by GOJO (www.gojo.com)**
October 25, 2018	*(FREE Teleclass)* **"AHEAD" – A CONSOLIDATED FRAMEWORK FOR BEHAVIOURAL INFECTIOUS RISKS IN ACUTE CARE**

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