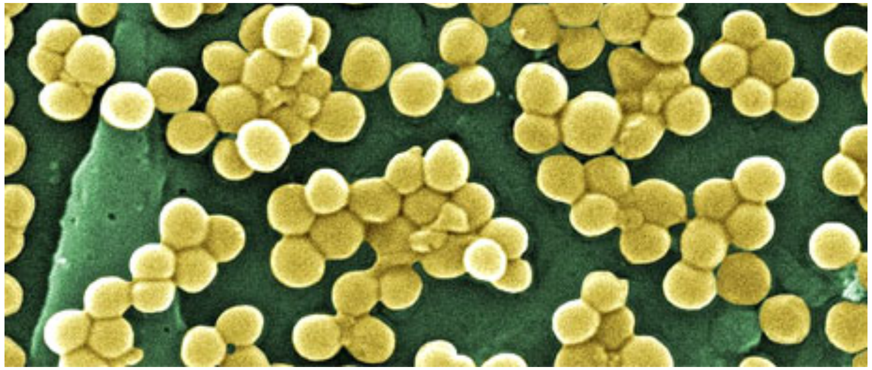
Desinfektionsmittel- und Antibiotika-Resistenz: Ein Zusammenhang?

Stephan Harbarth, MD MS



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Important points

- Antibiotic resistance is common and clinically more important than biocide resistance
- Resistance to disinfectants is not yet a major problem in healthcare
- Cross- and co-resistance between biocides and antibiotics exist and should be carefully monitored

The emergence of bacterial resistance/tolerance to biocides has been described in clinical isolates following:

- triclosan baths and hand wash

  Cookson BD, *et al. Lancet 1991;337:1548=9.*
  Webster J, *et al. J Paediatr Child Health 1994;30:59-64.*

- chlorhexidine use

  Nakahara H & Kozukue H. *Sbl Bakt Hyg, I. Abt Orig A 1981;251:177 -84.*
  Batra R *et al. Clin Infect Ds* 2010;50:210-7.
  Lee AS, *et al. Clin Infect Dis* 2011; 52:1422-30.

- QAC use

  Geftic SG, *et al. Appl Environ Microbiol 1979;39:505-10.*
  Wenzel RP, *et al. Am J Epidemiol 1976;*104:170-80.

- silver and silver sulfadiazine use

  Bridges K & Lowbury EJL. *J Clin Pathol 1977;30:160-74.*
  Silver S. *FEMS Microbiol Rev 2003;27:341-53.*

- iodophor use

  Anderson RL. *Infect Control Hosp Epidemiol 1989;10:443-6.*

Emergence of Glutaraldehyde-Resistant *Pseudomonas aeruginosa*

Sarah Tschudin-Sutter, MD;[1] Reno Frei, MD;[2] Günter Kampf, MD;[3,4] Michael Tamm, MD;[5] Eric Pflimlin, RN;[6]
Manuel Battegay, MD;[1] Andreas Franz Widmer, MD, MSc[1]

OBJECTIVE. In November 2009, routine sampling of endoscopes performed to monitor the effectiveness of the endoscope-cleaning procedure at our hospital detected *Pseudomonas aeruginosa*. Herein we report the results of the subsequent investigation.

DESIGN AND METHODS. The investigation included environmental cultures for source investigation, molecular analysis by pulsed-field gel electrophoresis (PFGE) to reveal the identity of the strains, and determination of the bactericidal activity of the glutaraldehyde-based disinfectant used for automated endoscope reprocessing. In addition, patient outcome was analyzed by medical chart review, and incidence rates of clinical samples with *P. aeruginosa* were compared.

SETTING. The University Hospital of Basel is an 855-bed tertiary care center in Basel, Switzerland. Approximately 1,700 flexible bronchoscopic, 2,500 gastroscopic, 1,400 colonoscopic, 140 endoscopic retrograde cholangiopancreatographic, and 140 endosonographic procedures are performed annually.

RESULTS. *P. aeruginosa* was detected in samples obtained from endoscopes in November 2009 for the first time since the initiation of surveillance in 2006. It was found in the rinsing water and in the drain of 1 of the 2 automated endoscope reprocessors. PFGE revealed 2 distinct *P. aeruginosa* strains, one in each reprocessor. The glutaraldehyde-based disinfectant showed no activity against the 2 pseudo-outbreak strains when used in the recommended concentration under standard conditions. After medical chart review, 6 patients with lower respiratory tract and bloodstream infections were identified as having a possible epidemiological link to the pseudo-outbreak strain.

CONCLUSIONS. This is the first description of a pseudo-outbreak caused by *P. aeruginosa* with reduced susceptibility to an aldehyde-based disinfectant routinely used in the automated processing of endoscopes.

Infect Control Hosp Epidemiol 2011;32(12):1173-1178

Tschudin-Sutter S, Infect Control Hosp Epidemiol 2011; 32: 1173-78

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TABLE 3. Bactericidal Tests with Glutaraldehyde (20 g/100 g) Applied for 10 Min at 20°C

Strain, glutaraldehyde concentration, %	Bacterial growth	Reduction factor of no. of CFU
Pseudomonas aeruginosa (strain A)		
0.5	Yes	<4.11
1.0	Yes	<4.11
2.0	Yes	<4.67
P. aeruginosa (strain B)		
0.5	Yes	<4.16
1.0	Yes	<4.16
2.0	Yes	<4.16
P. aeruginosa (ATCC 15442)		
0.5	No	>5.54
1.0	No	>5.54
2.0	No	>5.54

Tschudin-Sutter S, Infect Control Hosp Epidemiol 2011; 32: 1173-78

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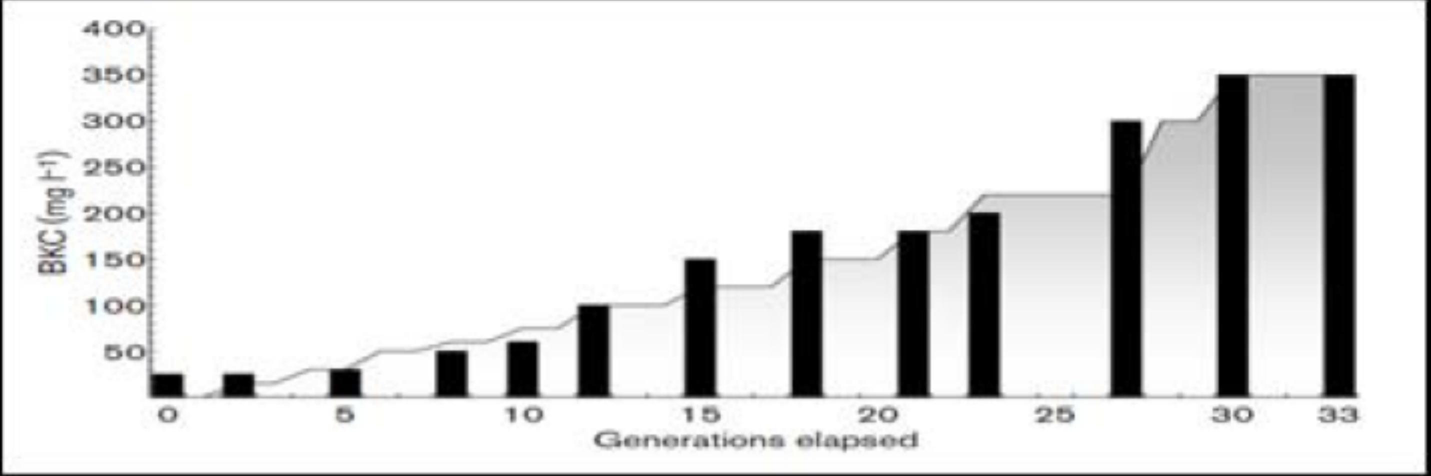
TABLE 2. Bactericidal Tests with Glutaraldehyde (20 g/100 g)Applied for 10 Min at 55°C

Strain, glutaraldehyde concentration, %	Bacterial growth	Reduction factor of no. of CFU
Pseudomonas aeruginosa (strain A)		
0.5	Yes	<4.12
1.0	Yes	>5.50
2.0	No	>5.50
P. aeruginosa (strain B)		
0.5	Yes	<4.00
1.0	Yes	4.42
2.0	No	>5.39
P. aeruginosa (ATCC 15442)		
0.5	No	>5.55
1.0	No	>5.55
2.0	No	>5.55

Tschudin-Sutter S, Infect Control Hosp Epidemiol 2011; 32: 1173-78

Emergence of resistance to benzalkonium and ciprofloxacin in *P. aeruginosa*



MIC (mg BKC l⁻¹)	MIC using E-test methodology (mg l⁻¹)								
	MC	TOB	AZ	CIP	PB	AK	GE	VA	IP
25	>128	1.5	3	0.125	4	8	4	>128	2
40	>128	1.5	2	0.250	3	6	4	>128	1.5
50	96	1.5	3	2	3	6	4	>128	2
80	96	1	3	2	1.5	6	6	>128	1.5
180	96	1.5	2	8	1.5	4	4	>128	0.75
200	96	1.5	3	8	3	8	6	>128	0.75
300	48	1	2	16	3	6	4	>128	2
>350	48	1.5	2	32	1.5	8	6	>128	1.5
>350	16	1	3	32	2	6	6	>128	2

Mc Cay PH *et al*. *Microbiology* 2010;156:30–38.

Fact n°1

- MRSA ↓
- ESBL-producers ↑
- Carbapenem-resistant Gram-negatives ↑
- Multiresistant *Acinetobacter* spp ↑
- *Clostridium difficile* ↑

- Not an increasing problem because of cross-resistance to disinfectants

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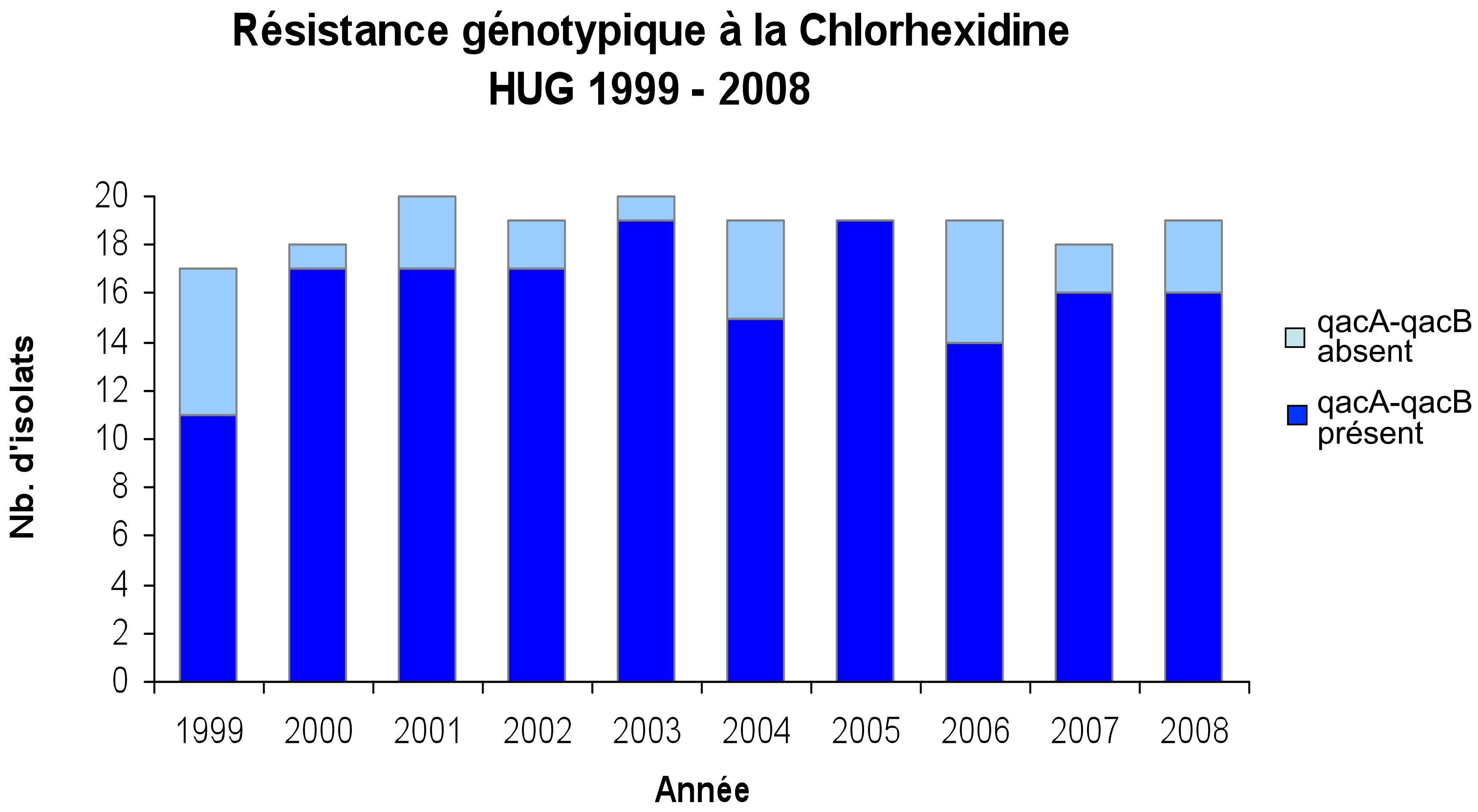
MRSA – Hémocultures



qacA-qacB dans 161 de 188 (86%) d'hémocultures

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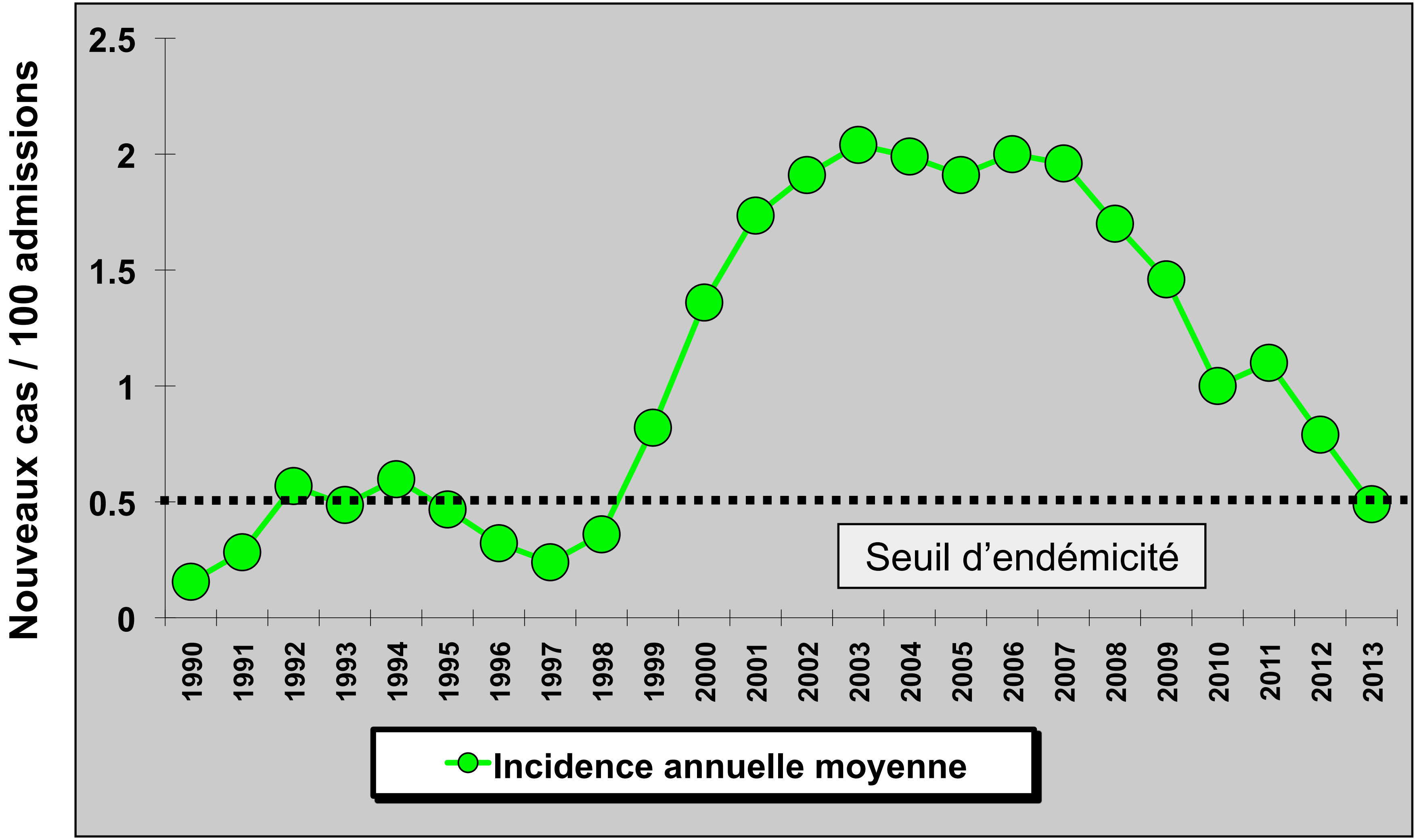
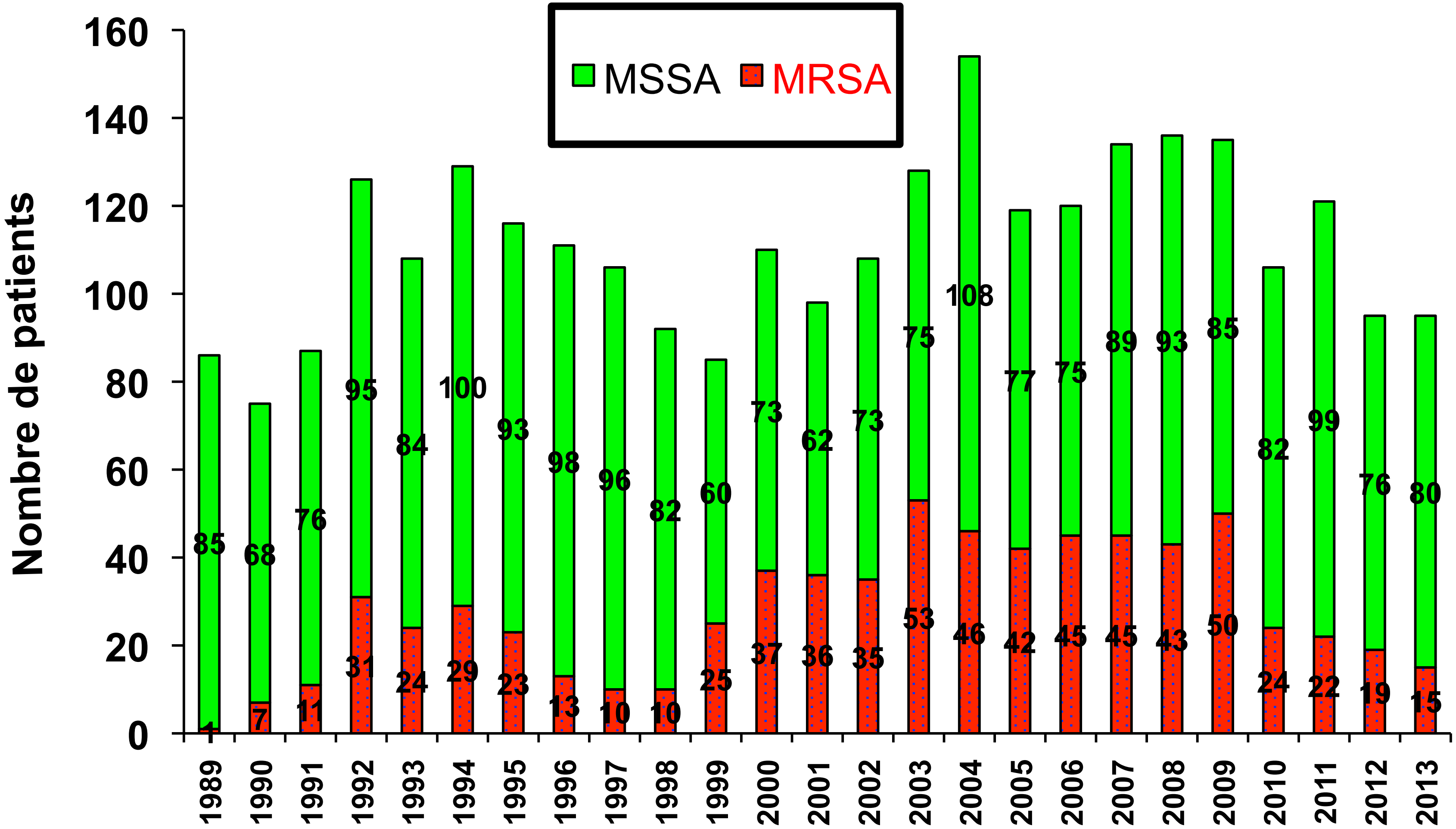
Incidence de nouveaux patients colonisés ou infectés par MRSA aux HUG, 1990 – 2013



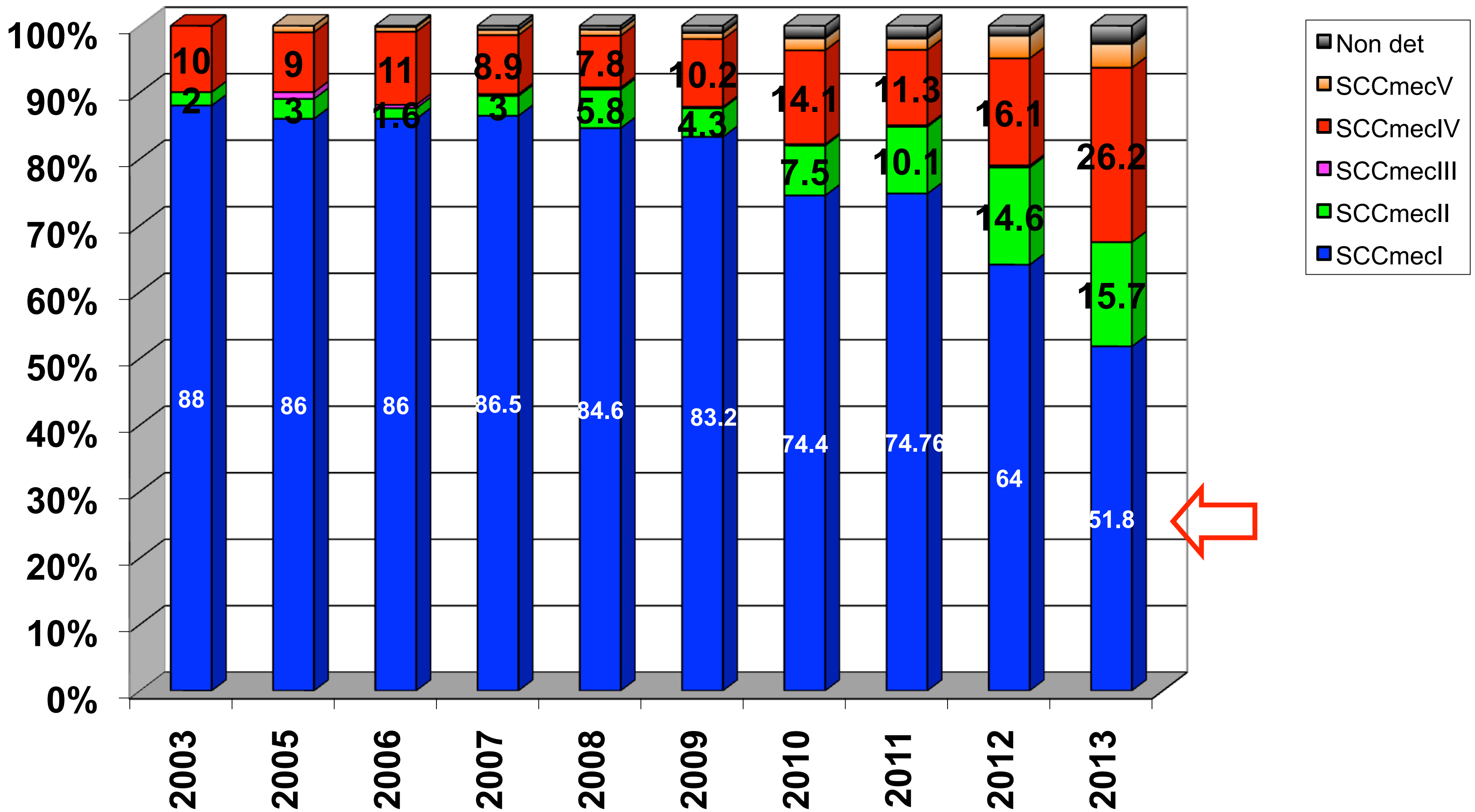
Service PCI - HUG

Bactériémies à *S. aureus*
HUG 1989 – 2013



Service PCI - HUG

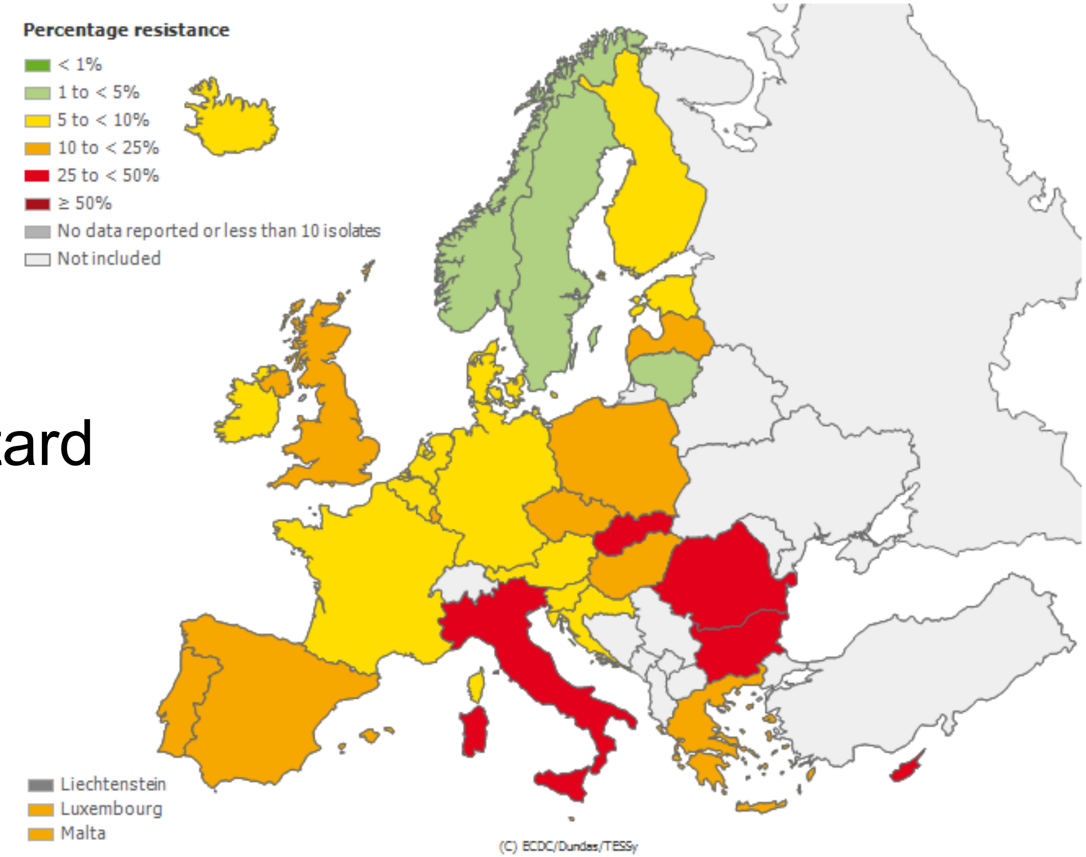
MRSA : Distribution des clones prédominants au sein des HUG, 2003-2013



Service PCI - HUG

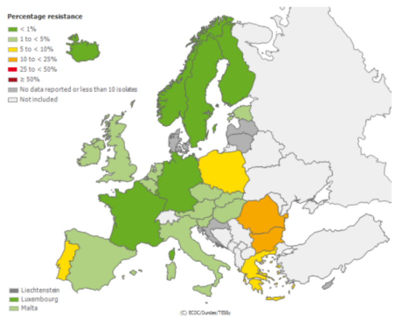
➢ Les BLSE sont en pleine augmentation au niveau mondial, européen ainsi qu'aux HUG.

Proportion of 3rd gen. cephalosporins Resistant (R) *Escherichia coli* Isolates in Participating Countries in 2012

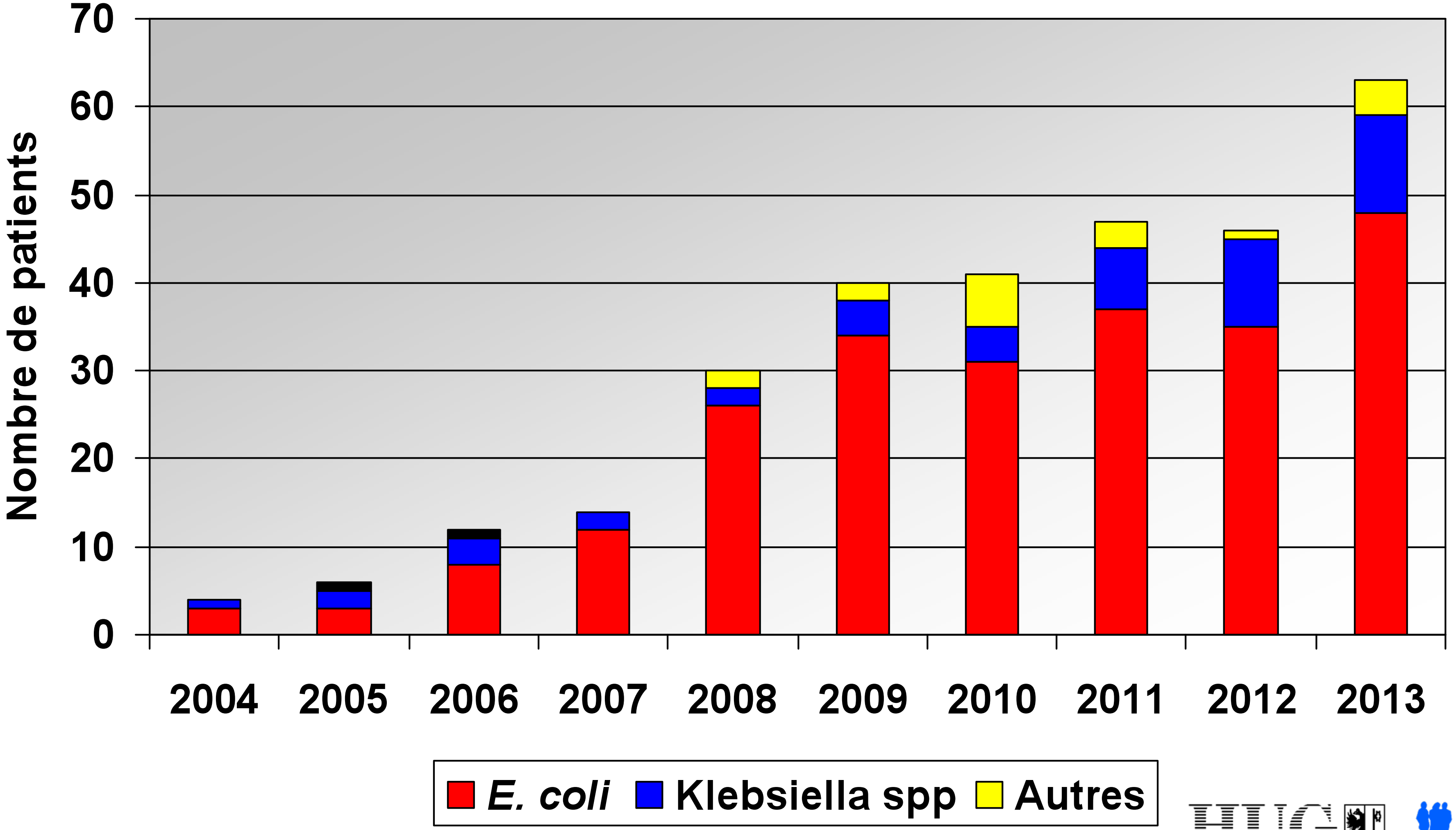


10 ans plus tard

Proportion of 3rd gen. cephalosporins Resistant (R) *Escherichia coli* Isolates in Participating Countries in 2002



Bactériémies à BLSE
HUG, 2004-2013



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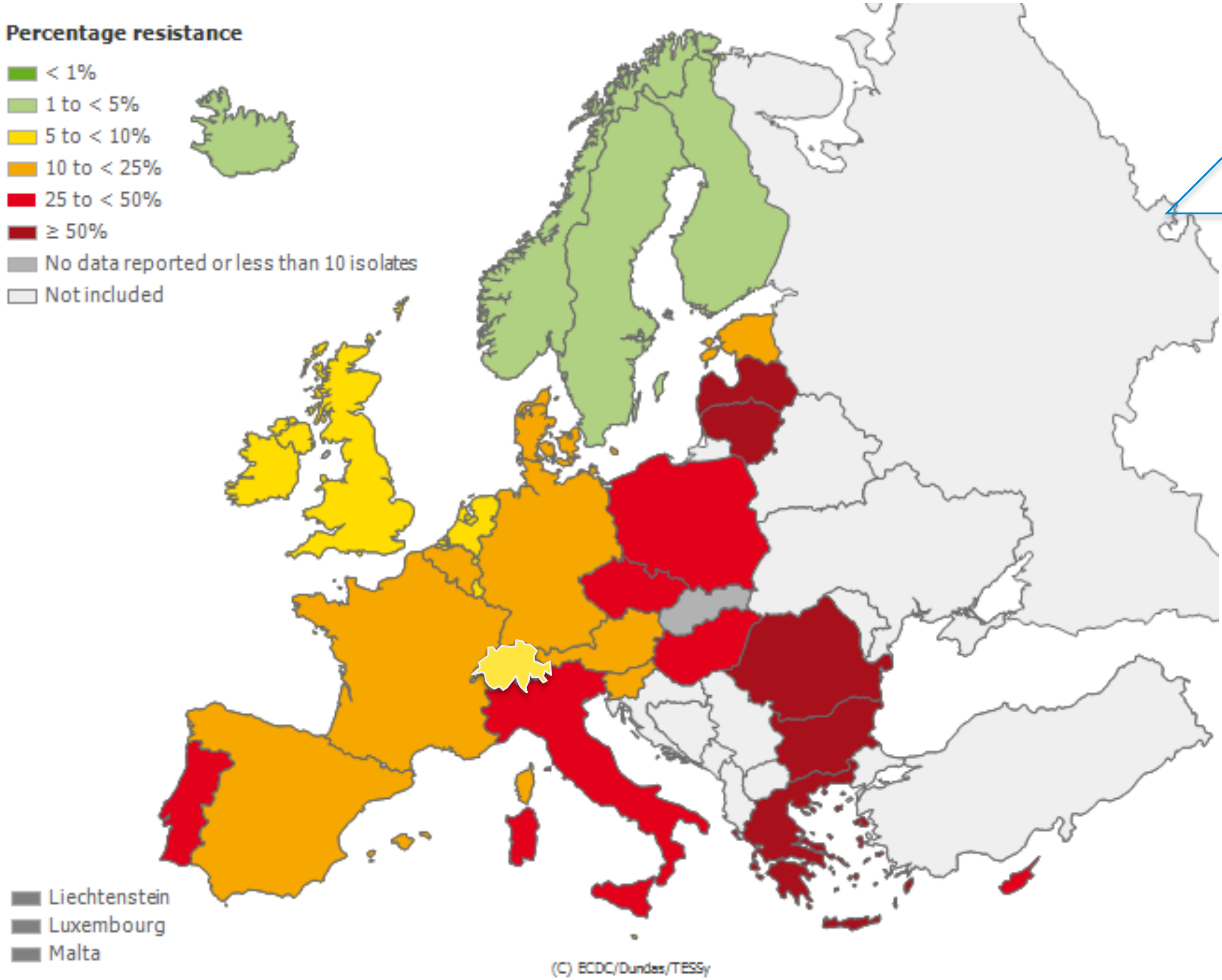
Klebsiella pneumoniae – 3rd Generation Cephalosporin Resistance in Europe - 2010



Euro Antimicrob Resist Surv Syst (EARSS) & anresis.ch

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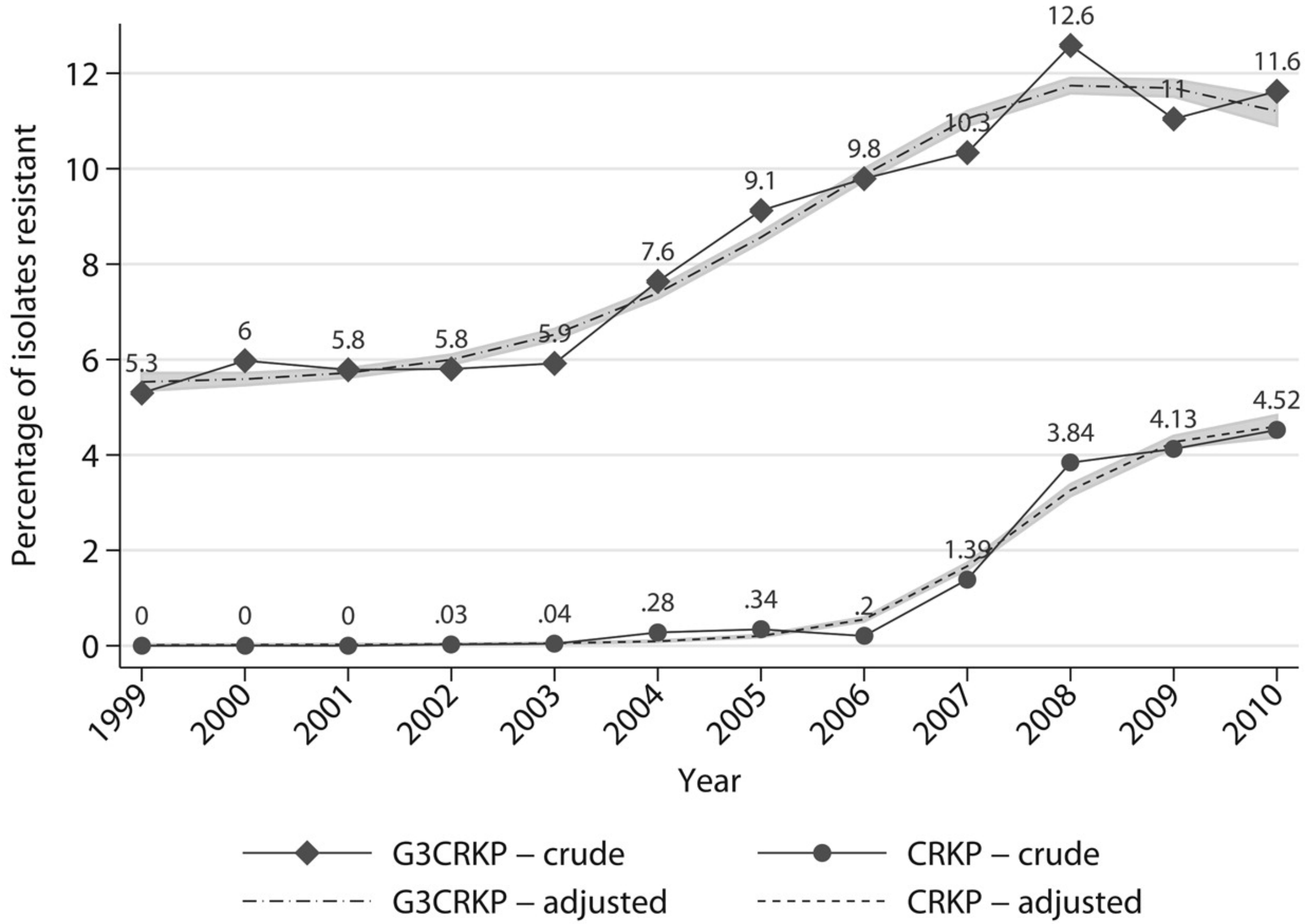
KPC in the U.S., 1999-2010



Braykov NP et al. Infect Control Hosp Epidemiol 2013; 34(3):259-268

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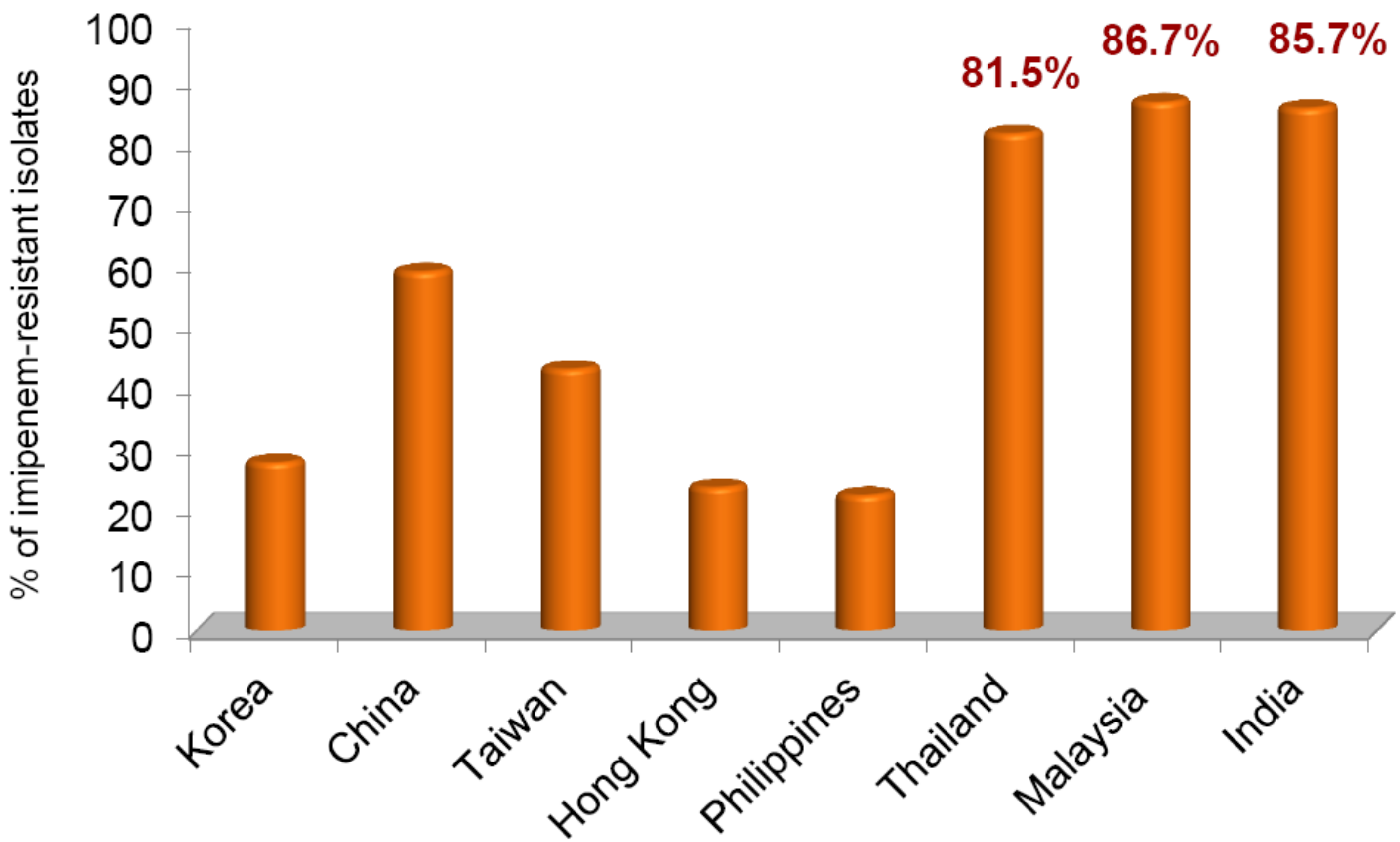
Antimicrobial resistance in Asia

Carbapenem-resistant *Acinetobacter* spp.

Extremely high prevalence of carbapenem resistance in Asian countries



APFID ASIA PACIFIC FOUNDATION FOR INFECTIOUS DISEASES

Courtesy:JH Song

Chung DR, Song JH, et al. Am J Respir Crit Care Med 2011;184:1409-1417

KPC & NDM control

- Routine disinfectants are effective against highly resistant carbapenamase-producing *Klebsiella pneumoniae* isolates

- Routine disinfection methods are effective to control outbreak of highly resistant organisms such as NDM-1 *Klebsiella* spp

VSW Koo, BJU International 2012; 110: E922-E926
A Robustillo Rodela et al. Euro Surveillance 2012; 17 (7): pii=20086

Agenda

- Antibiotic resistance is common and clinically more important
- **Resistance to disinfectants is <u>not</u> yet a major problem in healthcare**

Fact n°2

- Alcohol–based hand rubs do not exacerbate the spread of treatment-resistant pathogens, as the overuse of antibiotics does.
- Alcohol kills germs in a different way, by disrupting cell membranes, a process to which organisms are almost as unlikely to become immune as humans are to become immune against bullets.

D Owen. Annals of Health. The New Yorker, 4 March 2013.

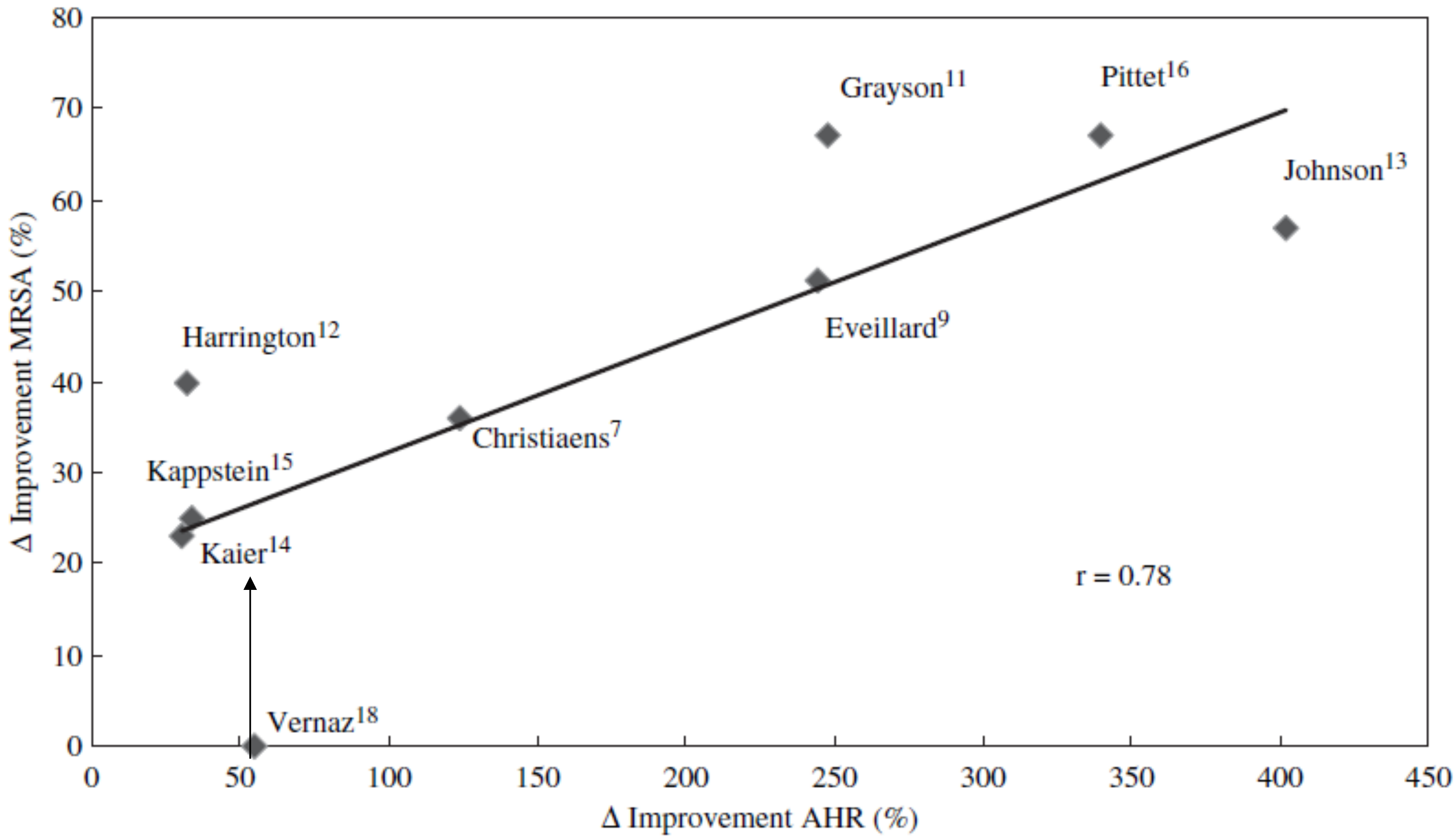


Figure 3 Difference (%) in the improvement of alcohol hand-rub (AHR) use and the change in meticillin-resistant *Staphylococcus aureus* (MRSA) rates (%) in studies from Table I. (%: MRSA parameter according to the endpoints in the studies.)

Sroka S et al, *J Hosp Infect* 2010; 74: 204-11

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Bacterial resistance to biocides in the healthcare environment: should it be of genuine concern?

- Microbial resistance to high or in-use concentration of biocides has been described in practice, although it remains very uncommon

- Antibiotic cross-resistance is <u>not</u> of genuine concern

Maillard JY. J Hosp Infect 2007; 65 (S2) 60–72

Does microbial resistance to biocides creates a hazard in infection control?

- The current risks to healthcare delivery caused by resistance related to biocides are low, provided that biocides are used under appropriate conditions.

Meyer B & Cookson B. J Hosp Infect. 2010; 76: 200-5

Fact n°3

- No data show that antibiotic-resistant bacteria are <u>less sensitive</u> to disinfectants than antibiotic-sensitive bacteria at currently used germicide contact conditions and concentrations

Susceptibility of antibiotic-susceptible and resistant hospital bacteria to disinfectants

- Study to compare susceptibility to disinfectants between antibiotic resistant bacteria (MRSA, VRE and *P. aeruginosa*) and antibiotic-susceptible bacteria
- Similar susceptibilities to phenolic and quaternary ammonium compounds

Rutala WA, Infect Control Hosp Epidemiol 1997; 18: 417-21

Bactericidal activities of disinfectants against VRE

- Assessment of the bactericidal activities of 35 commercially available disinfectants
- No differences in bactericidal time for activity against vancomycin-resistant versus vancomycin-susceptible enterococci
- VRE strains demonstrating slightly reduced susceptibility to germicides readily inactivated at concentrations of germicides used in hospitals

Y. Sakagami et al. J Hosp Infect 2002; 50: 140-144

Bacterial Contamination of Keyboards: Efficacy and Functional Impact of Disinfectants

- Disinfectants containing alcohol, chlorine, phenol or quaternary ammonium effective at removing MRSA, *P. aeruginosa* and VRE on contaminated PC keyboards
- Excellent sustained activity of quaternary ammonium–containing products against VRE and *P. aeruginosa* for up to 48 h

Rutala A et al; Infect Control Hosp Epidemiol 2006; 27: 372-377

Resistance to disinfectants in *Acinetobacter baumanii*

- Susceptibility of different strains of *Acinetobacter baumanii* to disinfectants –
  - 10 outbreak-related strains highly resistant to multiple antibiotics vs. 10 sporadic multi-susceptible isolates
  - No significant differences between the different disinfectants for both outbreak-related and sporadic *Acinetobacter baumanii*

Wisplinghoff H et al. J Hosp Infect 2007; 66: 174-181

Correlation between reduced susceptibility to disinfectants and multidrug resistance of *Acinetobacter*

- Testing susceptibility of 283 clinical isolates of *Acinetobacter* spp against 4 disinfectants:
  - Only 10% (28) of the isolates had reduced susceptibility to the disinfectants
  - MIC_{90} of the disinfectants was lower than their in-use concentration

Kawamura-Sato K et al. J Antimicrob Chemother 2012; 65: 1975-1983

Disinfection of MRSA in ICUs in Brazil

- Study on *Staphylococcus aureus* isolates in 2 Brazilian ICUs:
  - 36% resistant to oxacillin
  - 89% of these positive for mec A
- All tested disinfectants effective against *S.aureus* isolates
- No difference in resistance to disinfectants between MRSA and MSSA

Campos GB et al. New Microbiologica 2012; 35: 183-190

Fact n°4

- Cross- and co-resistance between antiseptics and antibiotics exists and should be carefully monitored

Relationship between biocide resistance and antibiotic resistance

- In laboratory experiments, antibiotic resistance following biocide exposure has been described:
  - **Cross-resistance**:

    selection of genes encoding resistance to both the biocidal substance and one or more antibiotics
  - **Co-resistance**: selection for clones or mobile elements also carrying antimicrobial resistance.
  - **Indirect selection** for bacterial sub-population following biocide exposure resulting in a decrease in susceptibility to both biocides and antibiotics.

Mechanisms

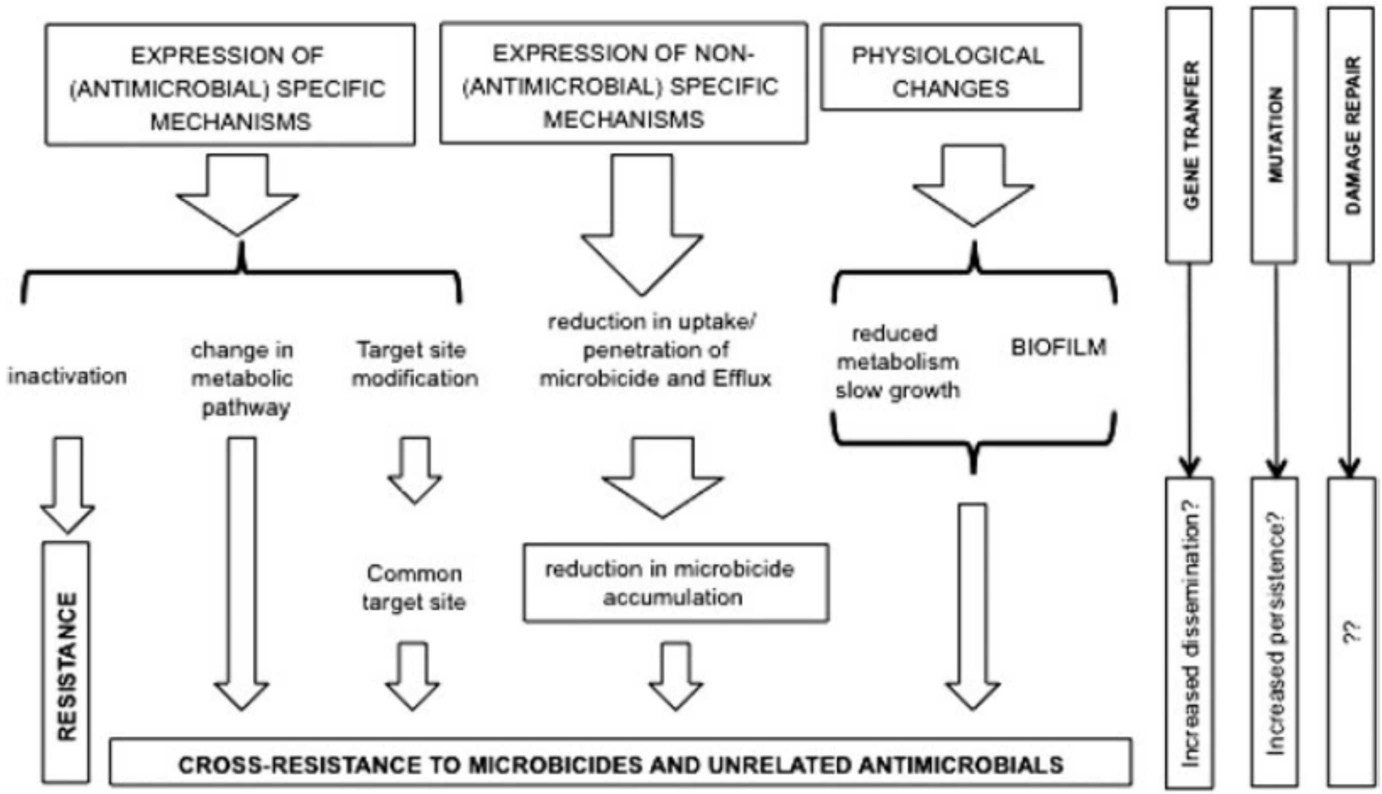


FIG. 1. Mechanisms leading to bacterial resistance and cross resistance to microbicides and unrelated antimicrobials.

Cross-resistance (1)

- Involves mainly **efflux pumps** mediating reduced susceptibility to several classes of antibiotics.

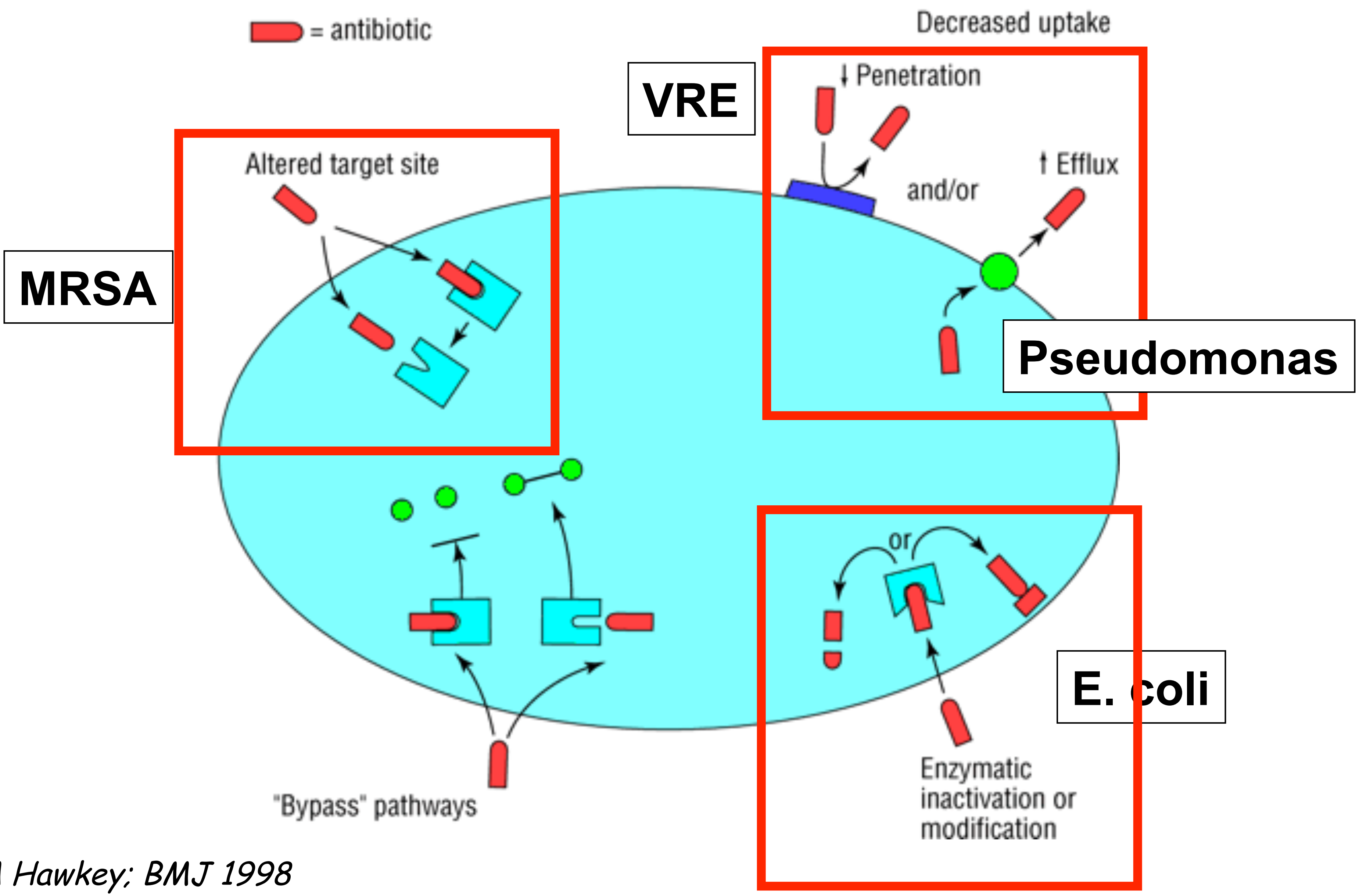
  Levy 2002, Piddock 2006, Thorrold et al. 2007

- Changes in **cell envelope**

  Denyer and Maillard 2002, Nikaido 2003, Tkachenko et al. 2007

- Role of **bacterial biofilms** in conferring resistance to both antibiotics and biocides

Mechanisms of antibiotic resistance



PM Hawkey; BMJ 1998

Cross-resistance (2)

- Experimental study in chicken carcasses

- Strains of *Salmonella typhimurium* that are resistant to antibiotics are not more resistant to chlorine in chilled water than strains of *Salmonella typhimurium* that are not resistant to antibiotics.

Oscar TP et al. J Food Prot. 2013; 76: 1031-4.

Co-resistance

- **Co-resistance**: mechanisms encoding **resistance** or reduced susceptibility are genetically linked
- **Tolerance** to **quaternary ammonium compounds** in Gram-negative **bacteria**.
  - *qac*-genes linked to sulphonamide resistance on mobile genetic elements

    (Sidhu et al. 2001, Sidhu et al. 2002)

Co-resistance

- **Co-resistance**: mechanisms encoding resistance are genetically linked
- Tolerance to quarternary ammonium compounds in Gram-negative bacteria
  - *qac*-genes linked to sulphonamide resistance on mobile genetic elements

Sidhu et al. 2001, Sidhu et al. 2002

Selection

- Clonal drift in the **bacterial** population towards bacterial **cells** that are more **resistant**.
  - Multi-drug resistant *Salmonella enterica* serovar Typhimurium DT104 caused an overall increase in the occurrence of resistance to antibiotics among *Salmonella* from food animals and humans in several countries

Doublet et al. 2003 & 2008

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Link between biocide and antibiotic resistance: open questions

- Impossible to determine which biocides create the highest risk of generating antibiotic resistance
- Horizontal gene transfer means that biocides could become triggers of bacterial resistance (e.g. triclosan)
- More data urgently needed

Summary

- Antibiotic resistance is common and clinically very important
- Increase in antibiotic resistance in clinically important bacteria is not associated with increasing resistance to biocides
- Resistance to disinfectants is not (yet) a major problem in healthcare
- Cross- and co-resistance between disinfectants and antibiotics exist and should be monitored

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Take home message

- ***There is scientific evidence that biocides select for biocide resistance, but that there is, so far, no conclusive evidence that this will determine an increase in antibiotic resistance.***

- **Workshop on biocides: do they select for antimicrobial resistance?** *Lisbon, Portugal, 21–23 November 2012*.

- **Published in: Recent advances in the potential interconnection between antimicrobial resistance to biocides and antibiotics.** April 2013, Vol. 11, No. 4 , Pages 363-366. http://informahealthcare.com/doi/abs/10.1586/eri.13.16

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Further Reading

EUROPEAN COMMISSION

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
- on consumer products
- on emerging and newly identified health risks
- on health and environmental risks

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Further Reading (2)

MICROBIAL DRUG RESISTANCE
Volume 19, Number 5, 2013

DOI: 10.1089/mdr.2013.0039

Does Microbicide Use in Consumer Products Promote Antimicrobial Resistance? A Critical Review and Recommendations for a Cohesive Approach to Risk Assessment

Jean-Yves Maillard,[1] Sally Bloomfield,[2] Joana Rosado Coelho,[3] Phillip Collier,[4] Barry Cookson,[5] Séamus Fanning,[6] Andrew Hill,[7] Philippe Hartemann,[8] Andrew J. Mcbain,[9] Marco Oggioni,[10] Syed Sattar,[11] Herbert P. Schweizer,[12] and John Threlfall[13]

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Evidence that Antimicrobial Resistance in Hospital Organisms Is Related to Use in Hospitals

- Reasonable biological model
- Consistent associations
- Dose-effect relationships
- Concomittant variations

Source: McGowan JE Jr. Bull NY Acad Med 1987;63:253-268.

Evolution of Antimicrobial Resistance

- “Natural” resistance
- Mutation/acquisition of resistance genes
- Amplification by antibiotic selection pressure
- Transmission & dissemination