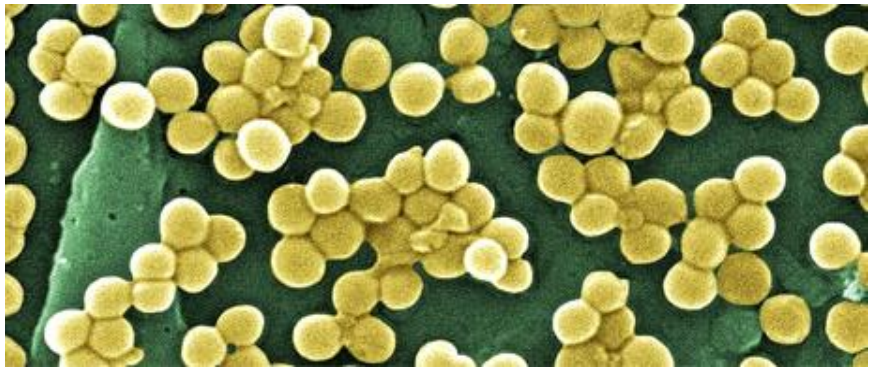
Is biocide resistance already a clinical problem?

Stephan Harbarth, MD MS



University of Geneva Hospitals and
Faculty of Medicine, Geneva, Switzerland

Hôpitaux Universitaires de Genève

Important points

- Biocide resistance exists
- Antibiotic resistance is common and clinically more important than biocide resistance
- Resistance to disinfectants is not yet a major clinical 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.*

Courtesy: M. Wilcox

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

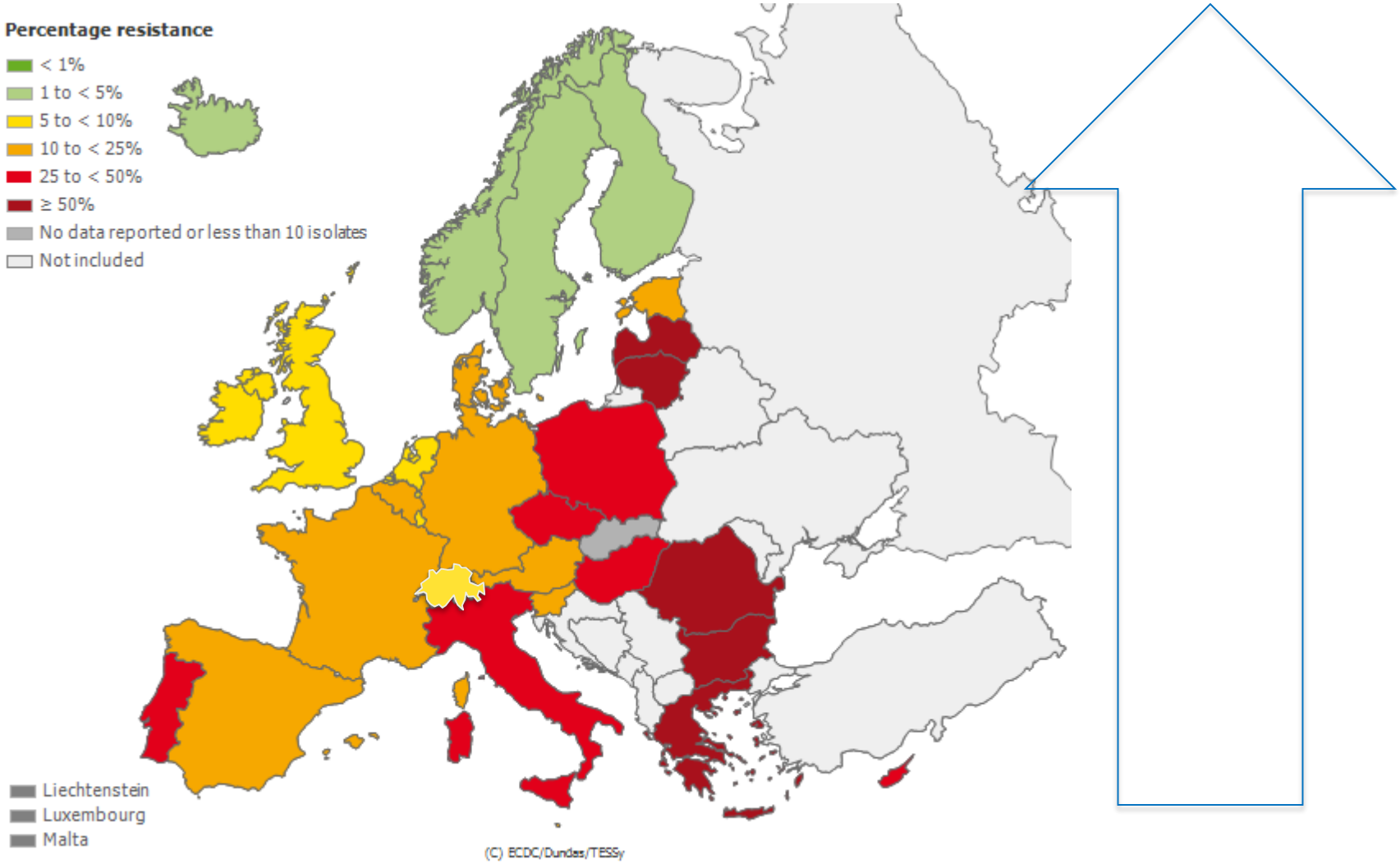
HUG
Hôpitaux Universitaires de Genève

Fact n°1: MDRO trends

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

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

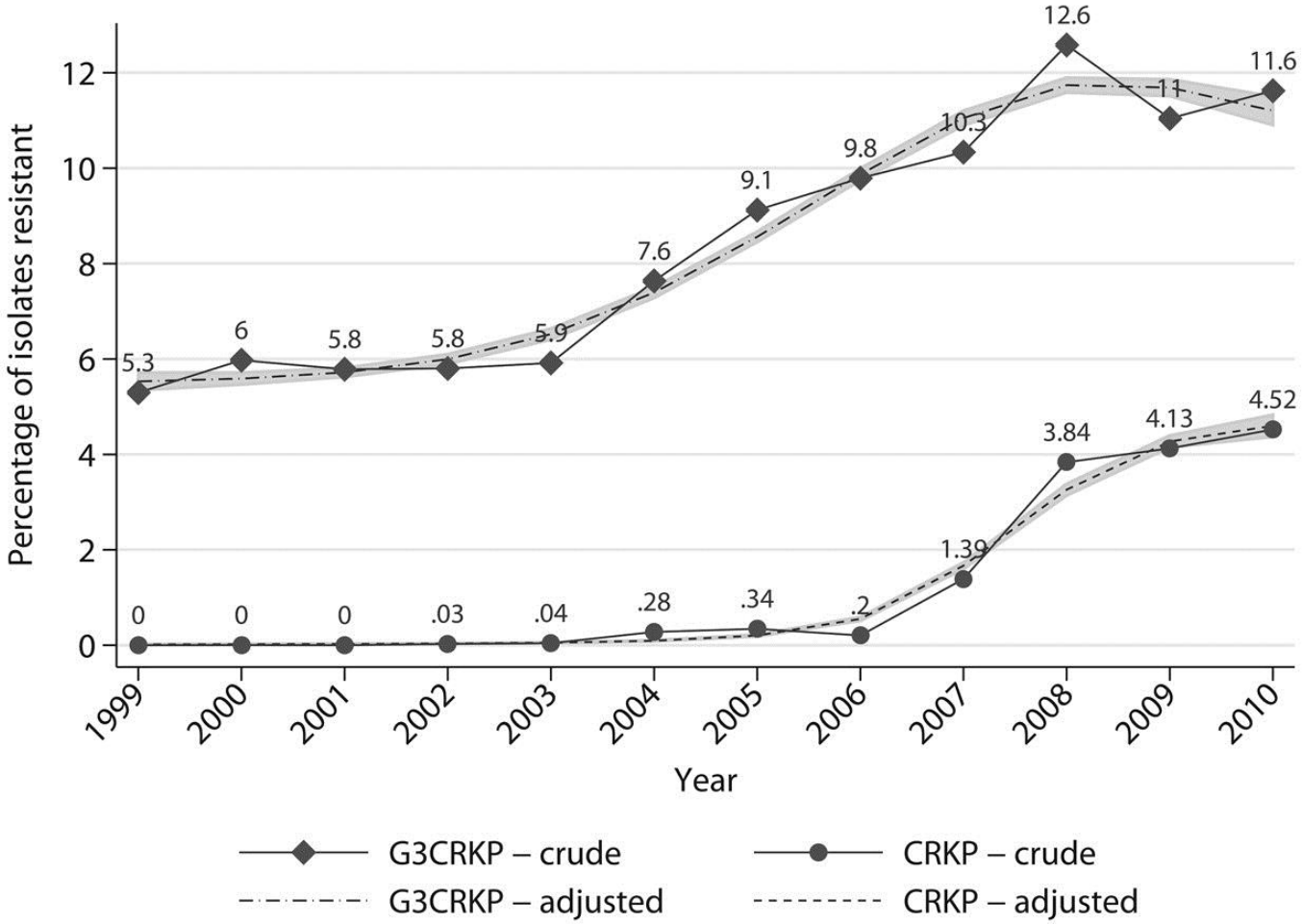
Klebsiella pneumoniae – 3rd Generation Cephalosporin Resistance in Europe - 2010



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

Hôpitaux Universitaires de Genève

KPC in the U.S., 1999-2010



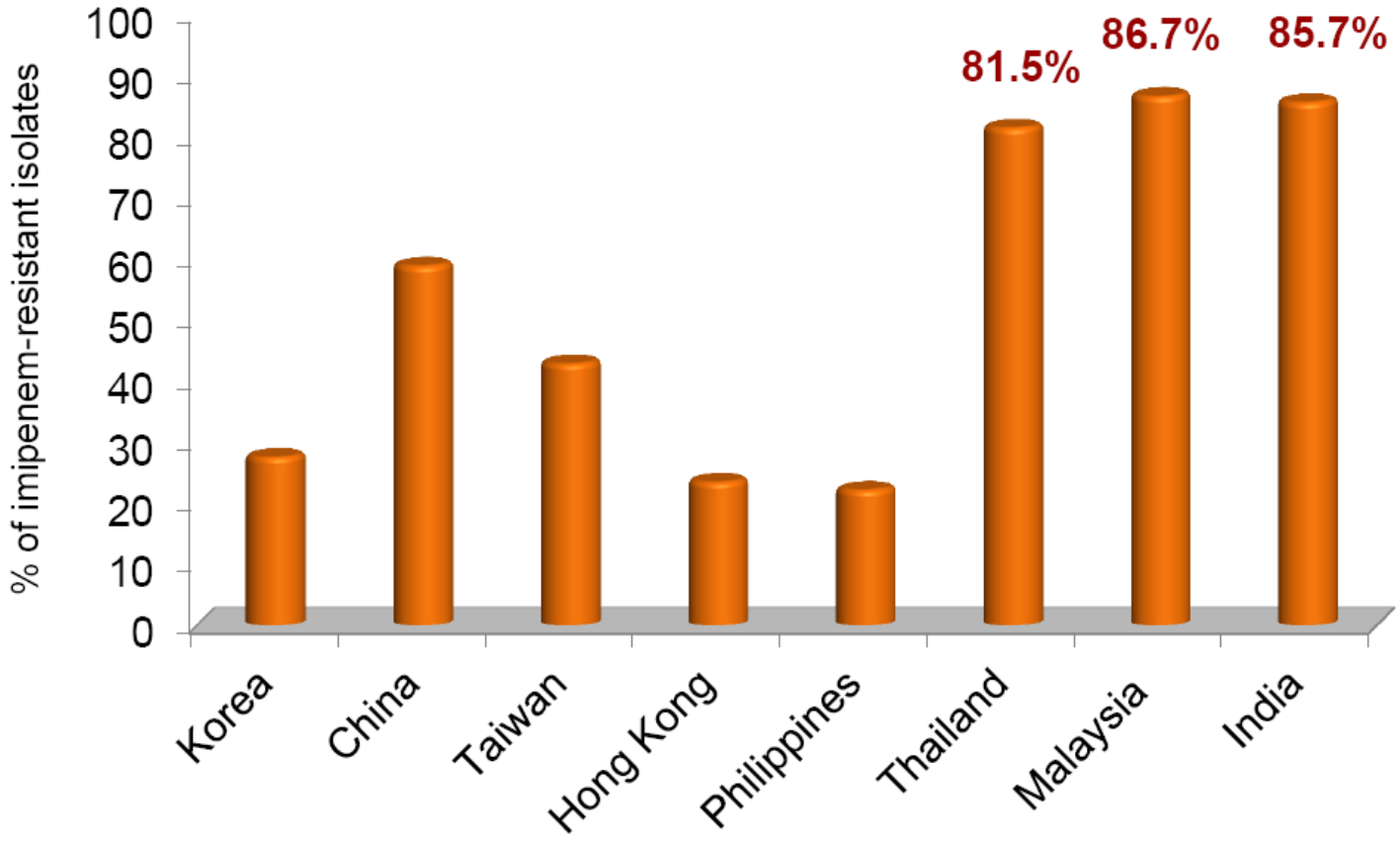
Braykov NP et al. Infect Control Hosp Epidemiol 2013; 34(3):259-268

Hôpitaux Universitaires de Genève

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* (KPC) isolates

- Routine disinfection methods are effective to control outbreaks 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**

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

Hôpitaux Universitaires de Genève

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.

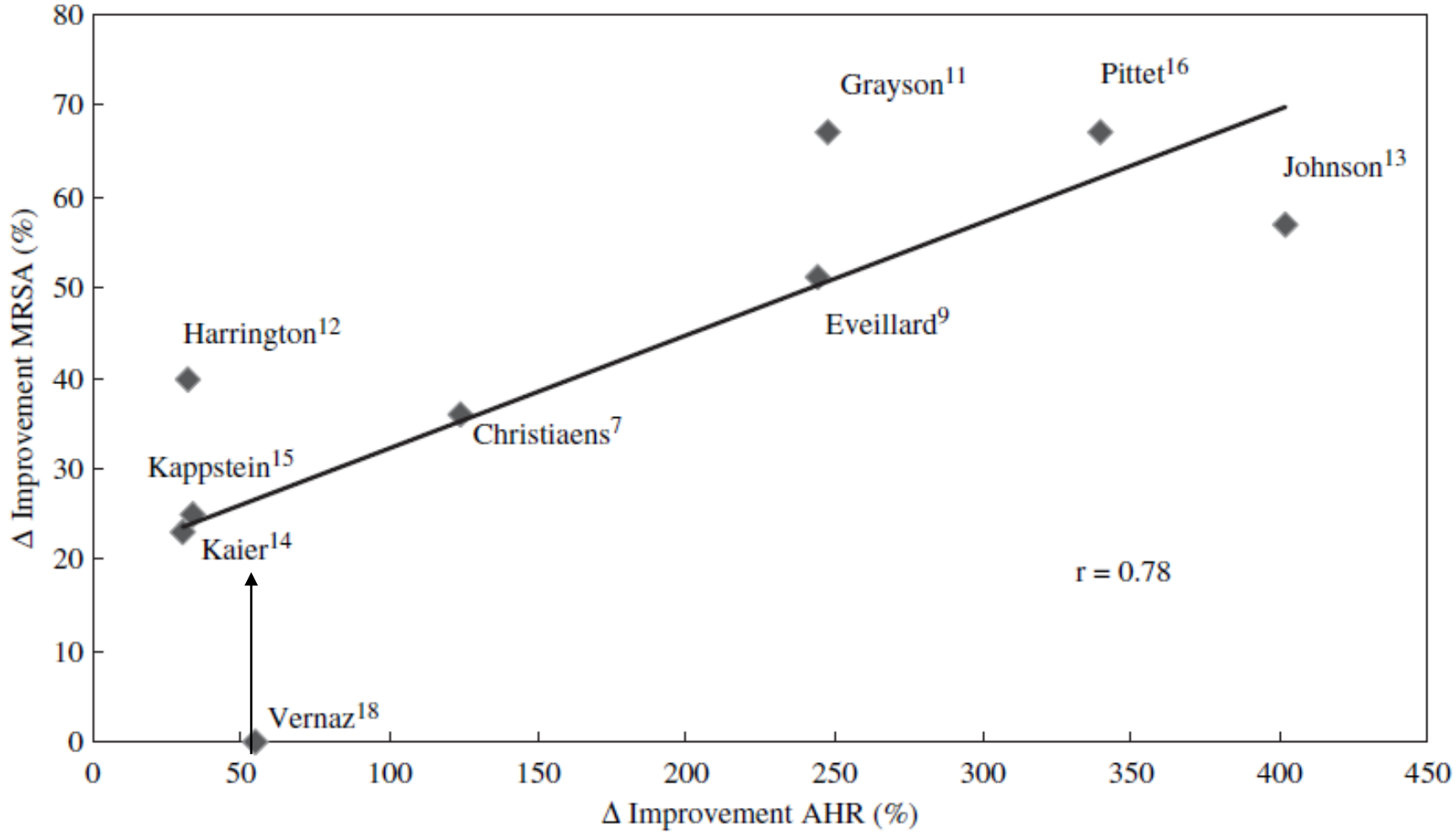


Figure 3 Difference (%) in the improvement of alcohol hand-rub (AHR) use and the change in meticillin-resistant *Staphylococcus aureus* (MRSA) rates (%) in studies from Table I. (%: MRSA parameter according to the endpoints in the studies

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

Chlorhexidine resistance

Are low-level mupirocin and chlorhexidine resistance associated with MRSA decolonisation failure ?

Lee & Harbarth. Clinical Infectious Diseases 2011;52(12):1422–1430

Independent risk factors associated with persistent MRSA colonization

	Multivariate analysis	
Risk factor	**OR (95% CI)**	**p value**
Mupirocin/chlorhex. resistance	**3.4 (1.5-7.8)**	**0.004**
Age (per 1 year increment)	1.04 (1.02-1.1)	0.001
Prior hospitalisation (2 years)	2.4 (1.1-5.7)	0.04
Wound/pressure sore	5.7 (1.8-17.6)	0.003
MRSA-inactive antibiotics	3.1 (1.3-7.2)	0.01
Central venous catheter	5.7 (1.4-23.9)	0.02

Lee & Harbarth. Clin Infect Dis 2011;52(12):1422–1430

HUG
Hôpitaux Universitaires de Genève

Efficacy and Limitation of a Chlorhexidine-Based Decolonization Strategy in Preventing Transmission of MRSA in an ICU

- Retrospective interrupted time-series study
- Reduced acquisition of endemic MRSA strain (IRR 0.3; 95% CI 0.19-0.47)
- 4-fold increased acquisition of epidemic MRSA strain
  - chlorhexidine MBCs increased 3-fold
  - Plasmid-borne gene: qacA/B

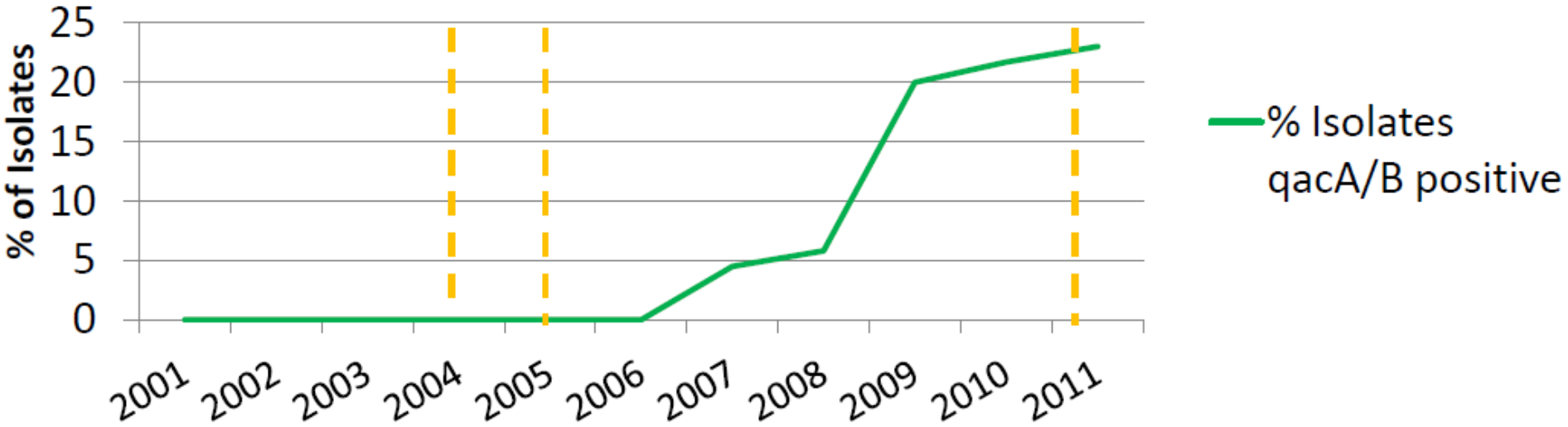
Batra R, Cooper BS, Whiteley C, et al. Clin Infect Dis 2010; 50: 210-217

Hôpitaux Universitaires de Genève

Staphylococcus aureus Infections in Pediatric Oncology Patients: High Rates of Antimicrobial Resistance, Antiseptic Tolerance and Complications

J. Chase McNeil, MD, Kristina G. Hulten, PhD,* Sheldon L. Kaplan, MD,* Donald H. Mahoney, MD,† and Edward O. Mason, PhD**

2004: CHX as skin cleanser of choice for CVLs and PACs.
2005: CHX mouthwash instituted for all AML patients daily.
2011: Daily CHX bathes for neutropenic AML patients.



Pediatr Infect Dis J 2013; 32: 124–128

Hôpitaux Universitaires de Genève

Fact n°3

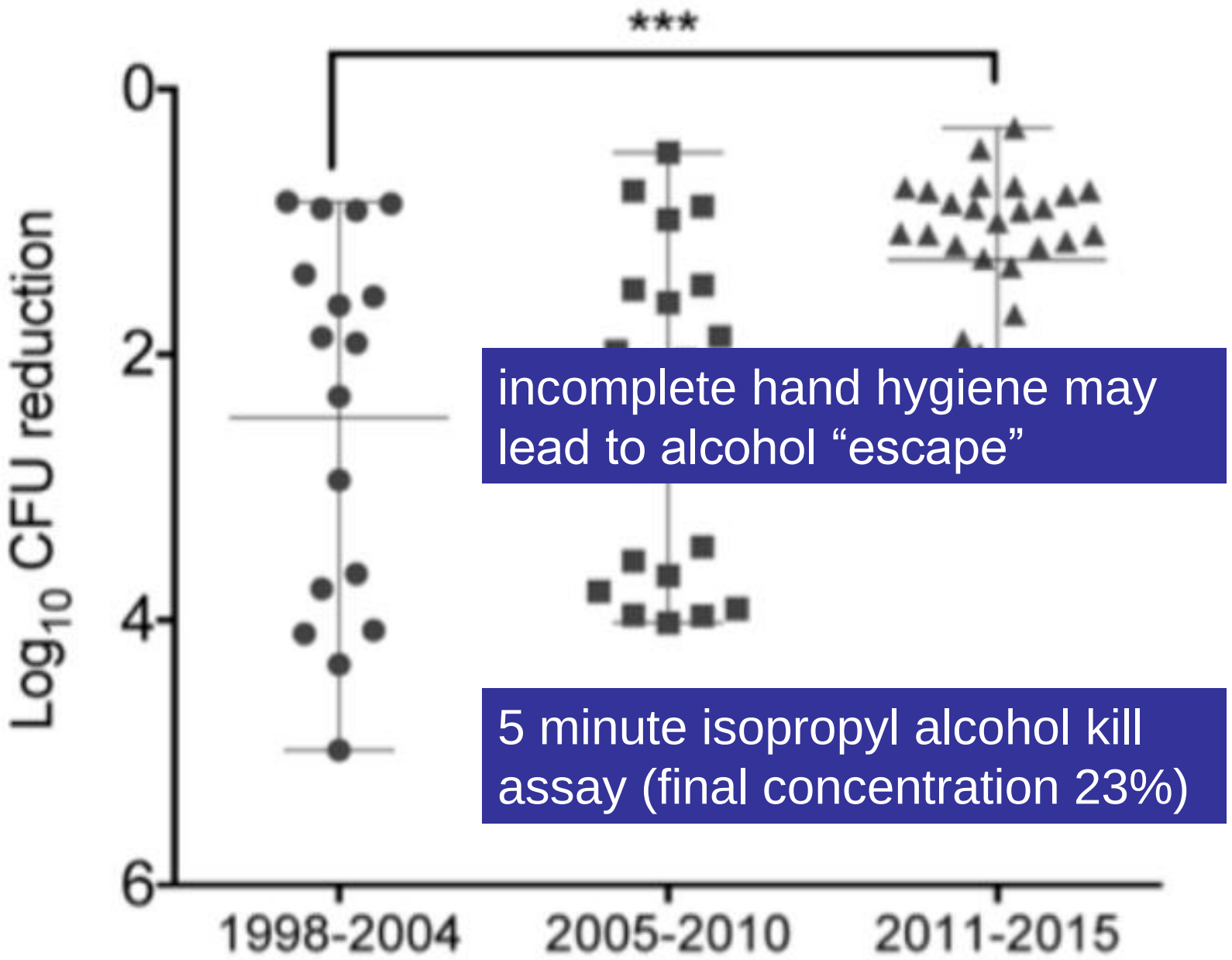
- No data show that antibiotic-resistant bacteria are less sensitive to disinfectants than antibiotic-sensitive bacteria at currently used germicide contact conditions and concentrations

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

E.faecium BSI isolates, Austin Hospital by time and alcohol log kill



incomplete hand hygiene may lead to alcohol “escape”

5 minute isopropyl alcohol kill assay (final concentration 23%)

Courtesy: P Johnson

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

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

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.

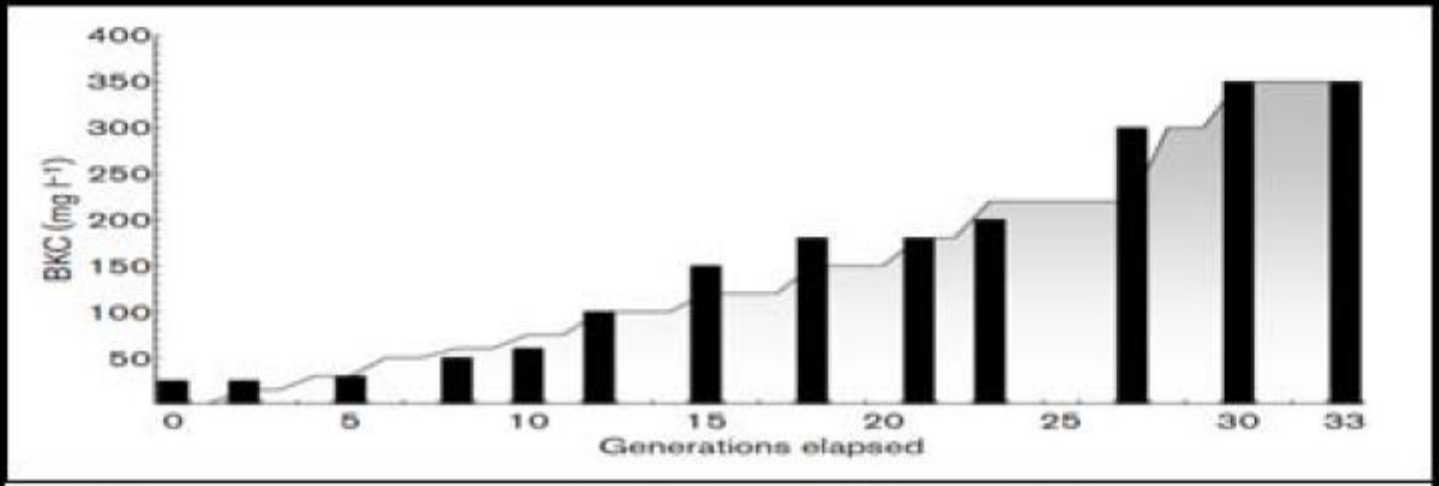
Co-resistance

- **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

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

Courtesy: M. Wilcox

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

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

- Biocide resistance exists, but antibiotic resistance is clinically more 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
  - CAVE: Chlorhexidine resistance
- Cross- and co-resistance between disinfectants and antibiotics exist and should be monitored

Further Reading

Journal of Hospital Infection 87 (2014) 194–202

Available online at www.sciencedirect.com

Journal of Hospital Infection

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

Review

Is reduced susceptibility to disinfectants and antiseptics a risk in healthcare settings? A point/counterpoint review

S. Harbarth [a], S. Tuan Soh [b], C. Horner [c], M.H. Wilcox [c,*]

[a] Geneva University Hospitals and Medical School, Geneva, Switzerland
[b] Hospital Buloh, Kuala Lumpur, Malaysia
[c] Leeds Teaching Hospitals and University of Leeds, Leeds, UK

Hôpitaux Universitaires de Genève

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]

HUG
Hôpitaux Universitaires de Genève