BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY

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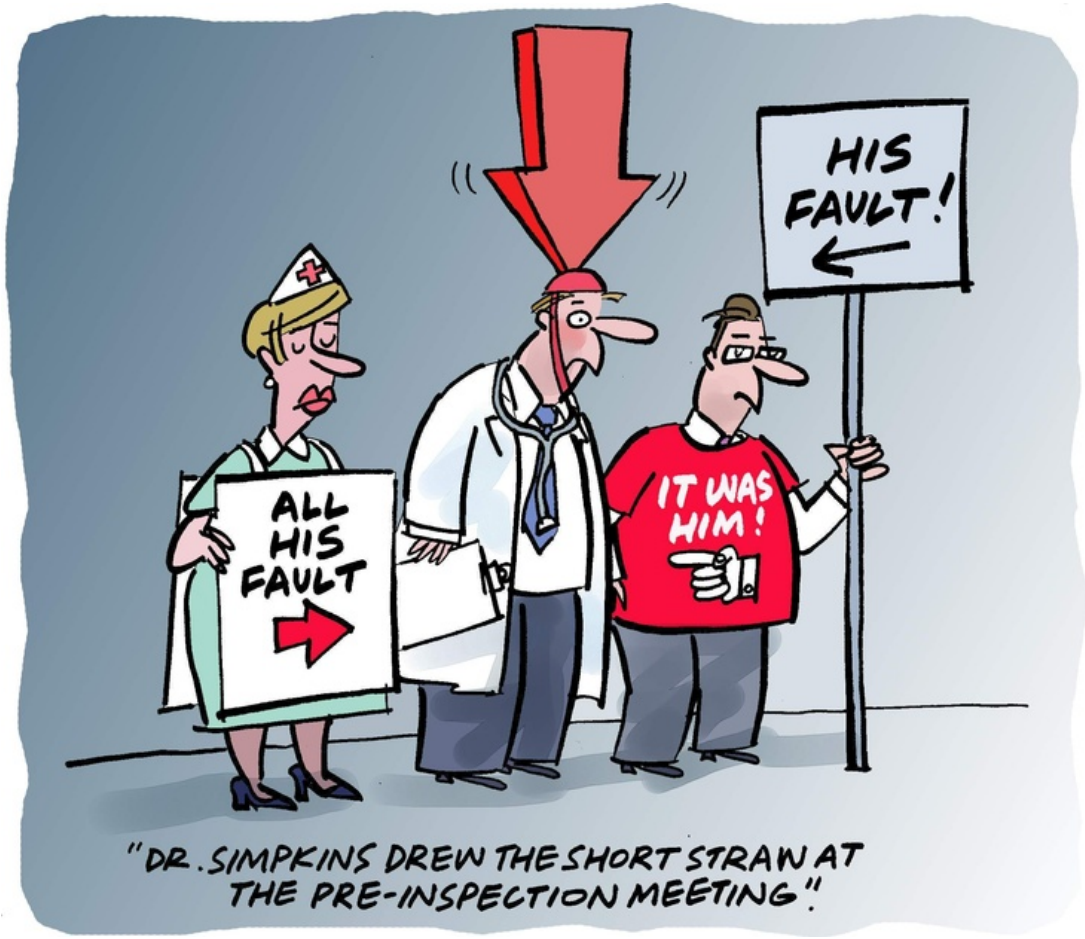
Debate: Conservation of antibiotics - reserving versus heterogenicity

Dr Nick Brown &

Professor Philip Howard

Debate

- Conservation of antibiotics is the ONLY way forward
- Heterogeneity: A little bit of everything will work wonders (cycling antibiotics is the future!)



Do you know how diverse you antibiotic prescribing is?

- Do you know your DU90?
  - No of AB that make up 90% of your consumption
- Do you know your antibiotic heterogeneity index?
  - No of AB >10% of total use compared to peers.
  - AHI = 0-1 with 1 being most diversity
- Do you even look at your resistance rates vs consumption?

Your Trust's Antimicrobial Homogeneity Index (AHI) for the chosen filters is

0.85

Peers

$$AHI = 1 - \{n/[2 \times (n-1)]\} \times \sum(a_i - b_i)$$

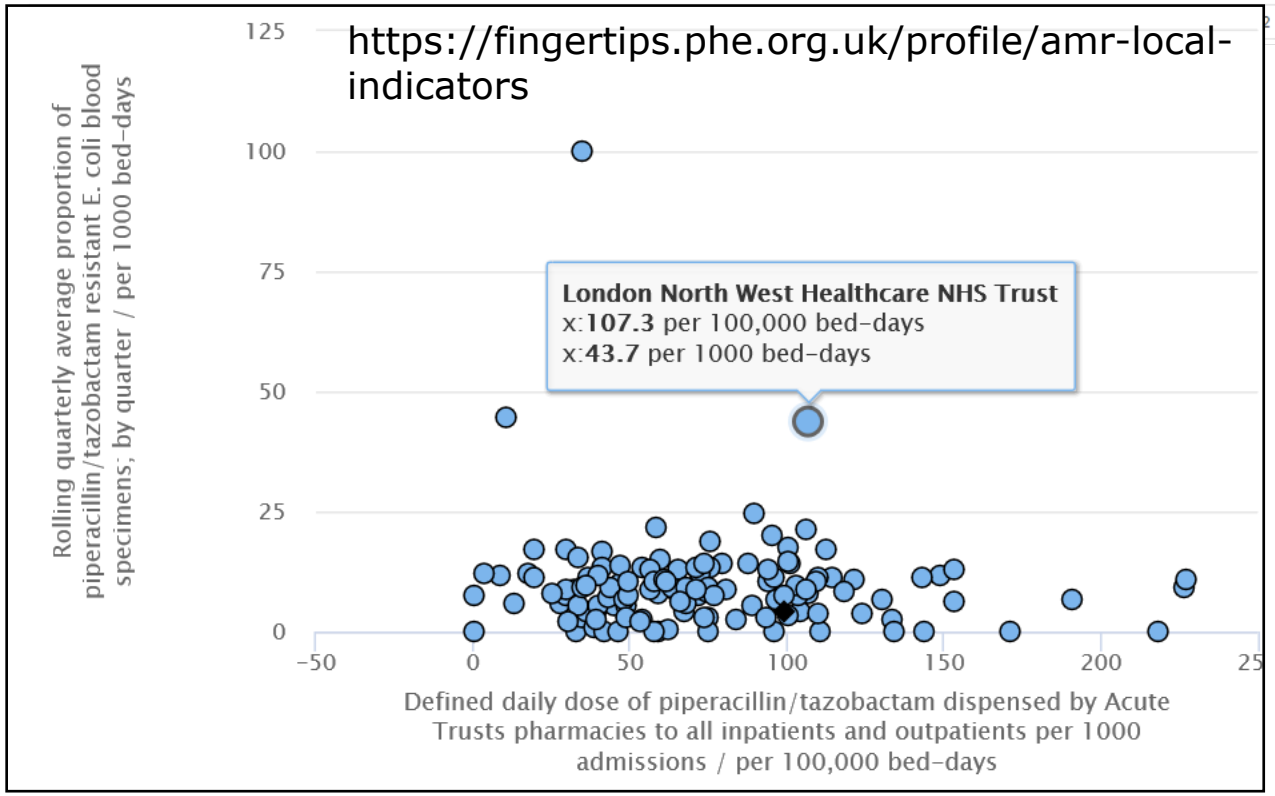
n Number of chemicals considered $\mathbf{a}_i$ Mean Proportion of Peers $\mathbf{b}_i$ Trust's Proportion

Total Antimicrobial DDDs (ATC J01)	777,908.63
Calculated for Chemicals with Proportion greater than	0 % Update

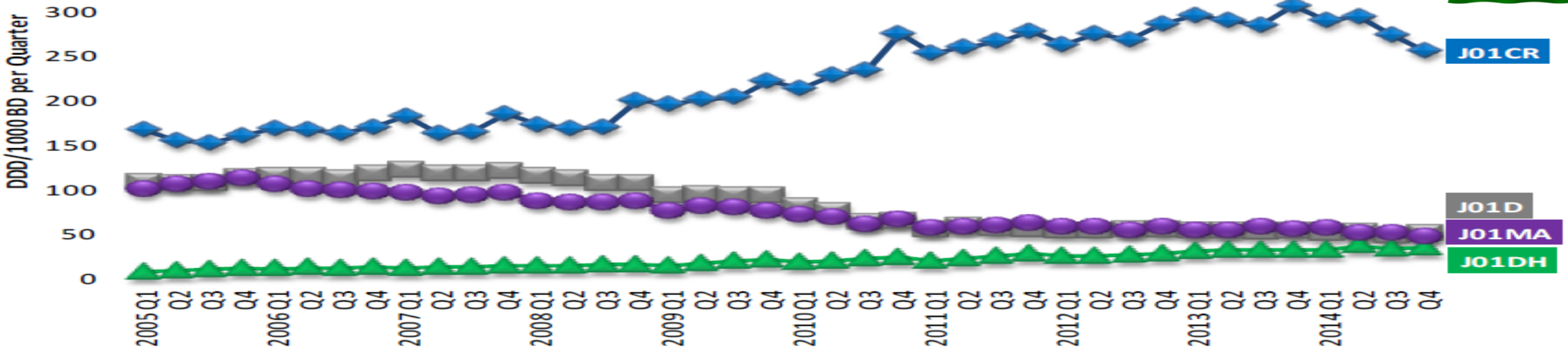
Chemicals Considered in Calculation 53

Chemical	DDDs	Proportion %	Peers' Proportion %	Difference
Amoxicillin and enzyme inhibitor	130,108.42	16.725	22.611	▼5.886
Flucloxacillin	114,294.00	14.692	9.777	▲4.915
Amoxicillin	81,071.25	10.422	9.906	▲0.515
Clarithromycin	57,347.95	7.372	7.154	▲0.218

https://fingertips.phe.org.uk/profile/amr-local-indicators



NHS Wales – impact of switching from cefalosporins & Fluoroquinolones to co-amoxiclav



Amoxicillin-clavulanate (J01CR/COA)

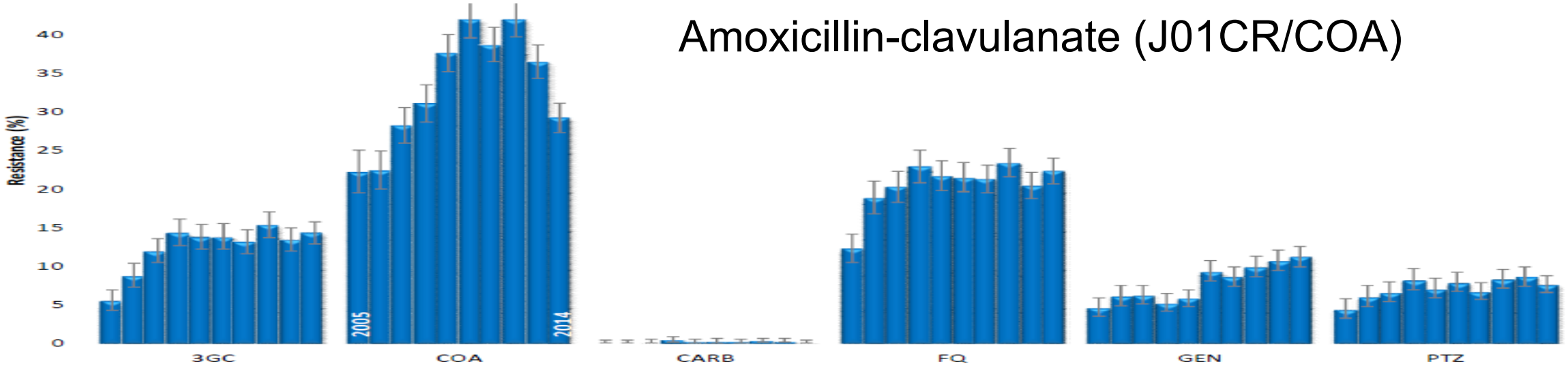


Figure 1: All-Wales resistance rates for *E. coli* bacteraemia (2005 to 2014).

Antibiotic heterogeneity

- since 1980s, concept of rotating antibiotic treatments for patients with bacterial infections has been viewed as a potential strategy for slowing emergence and spread of antibiotic resistance rates in hospitals.
- **Antibiotic cycling**: crop rotation idea applied to antibiotics.
  - Different antibiotics are prioritized against specific infections for a period of time (often months) before planned change to next antibiotic. Usually ITU.
  - Hoped that cycling would select against resistance alleles because one particular drug would not be encountered by a pathogen during a restriction cycle and so resistance would “reverse” because of the fitness costs of being drug-resistant
- **Antibiotic mixing** takes a less structured approach, with each consecutive patient on a ward or in a GP practice being treated with an alternative class of antibiotic.

Why restrict broad spectrum antibiotics? Selection risks associated with antimicrobial classes

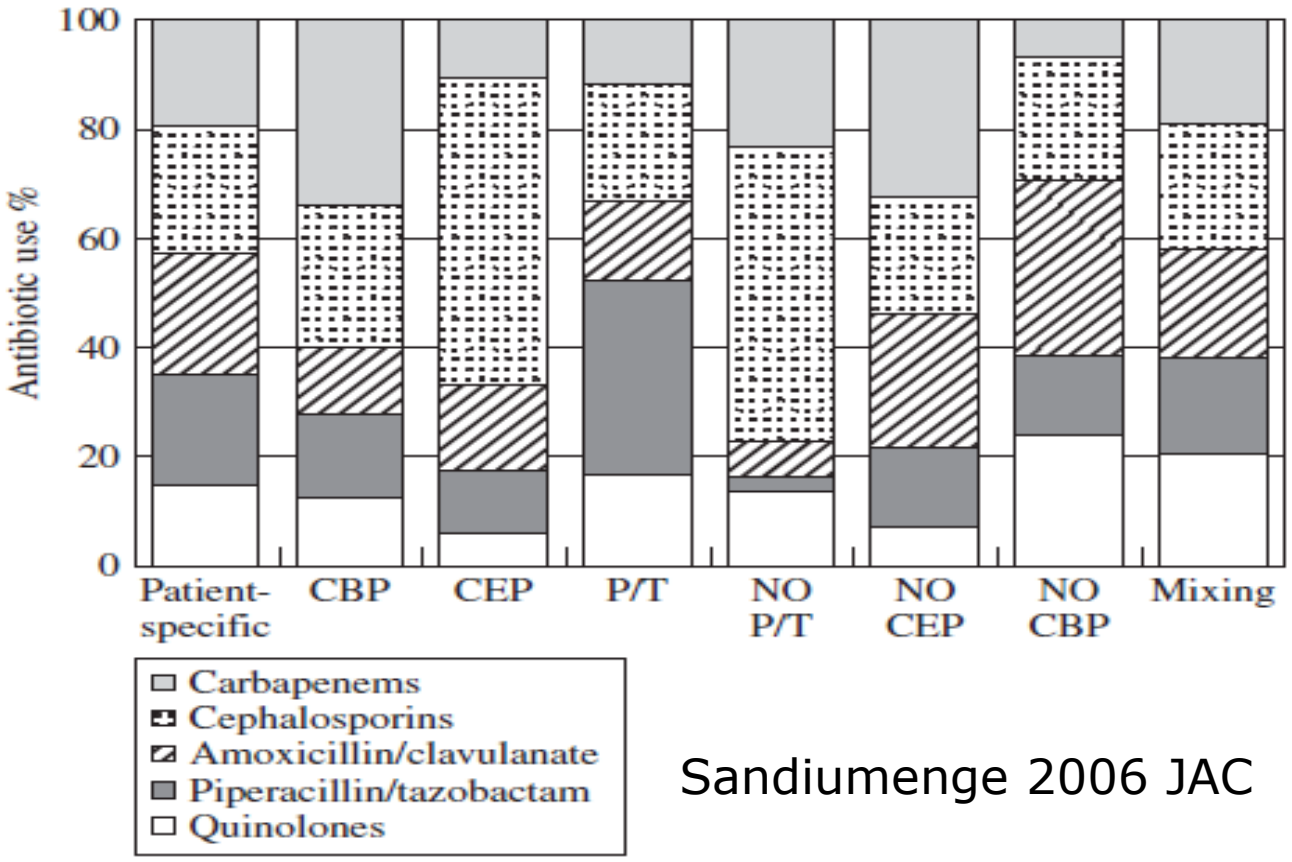
Darker the colour = higher risk	MRSA	VRE	ESBL	MDR Pseudomonas	Cdifficile	Carbapenemases
Carbapenems						
Piperacillin – tazobactam						
3rd Gen Cefalosporins						
Quinolones						
Tigecycline						

Antibiotic Chemotherapy 7th edition. Ed Davey P, Irving W, Thwaites G, Wilcox MH Oxford University Press 2015

Diversity strategies for VAP acquisition

4 strategies:

1. **Patient specific strategy** (based on prev AB and LOS) for 10 months
2. **Prioritisation** (4 months each): carbapenem , ant-Pseud cephalosporii and piperacillin-tazo
3. **Restriction** (4 months each): no CBP, no CEP, no P-T
4. **Mixing**: pre-established schedule by patient: antipseudomonal carbapenems then ciprofloxacin + clindamycin then antipseudomonal cephalosporins then piperacillin/tazobactam etc

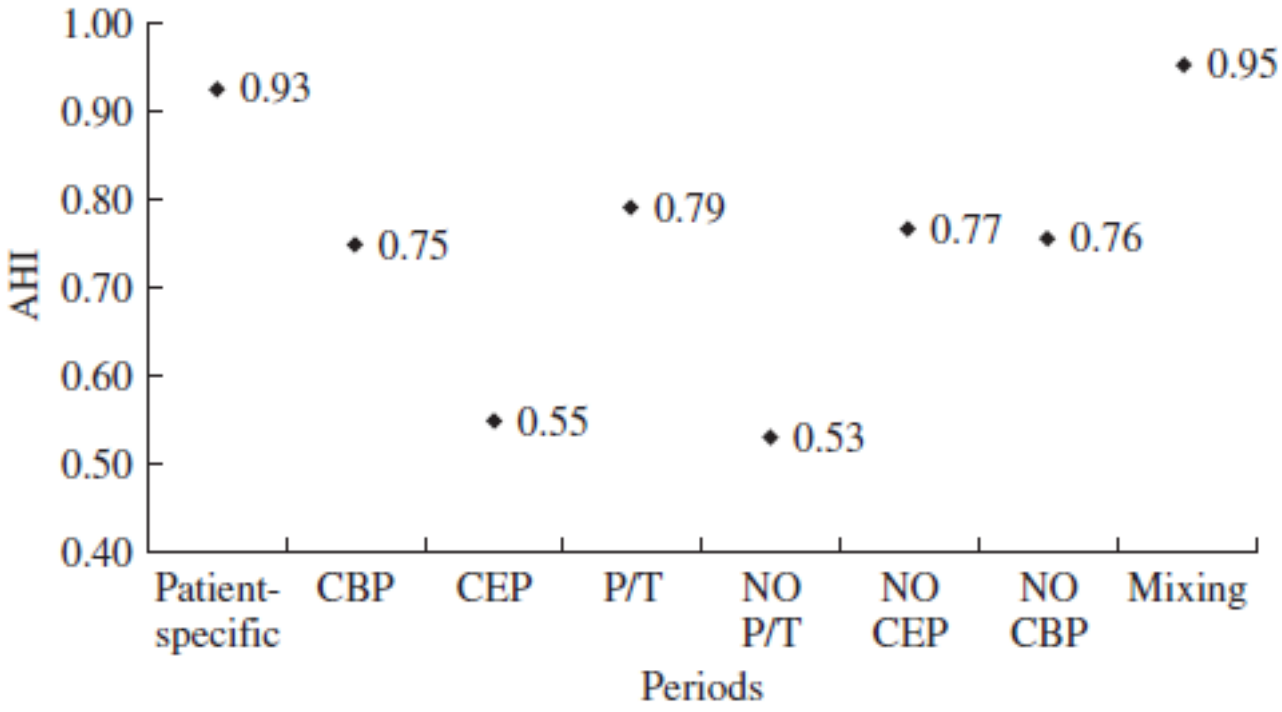


Sandiumenge 2006 JAC

Diversity strategies for VAP acquisition

High homogeneity (lower AHI) was associated with increases in

- carbapenem-resistant Acinetobacter baumannii (CR-Ab) (RR) 15.5; 95%CI 5.5–42.8],
- extended-spectrum b-lactamase (ESBL)-producing Enterobacteriaceae (RR 4.2; 95%CI 1.9–9.3) and
- Enterococcus faecalis (RR 1.7; 95%CI 1.1–2.9)



Sandiumenge 2006 JAC

CHEST

Original Research

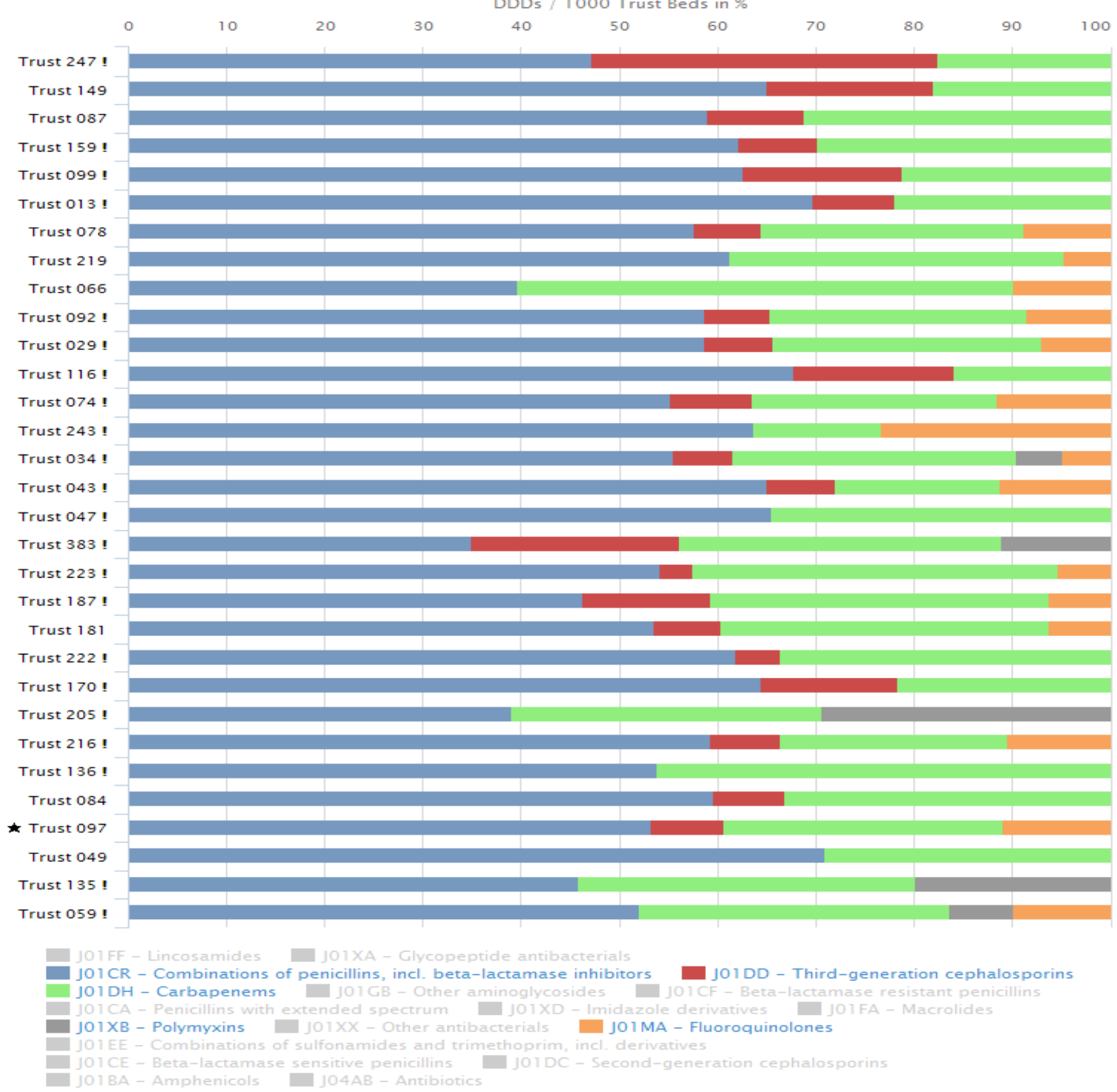
CRITICAL CARE

Effect of Antibiotic Diversity on Ventilator-Associated Pneumonia Caused by ESKAPE Organisms

2011

Alberto Sandiumenge, MD, PhD; Thiago Lisboa, MD; Frederic Gomez, MD; Pilar Hernandez; Laura Canadell, PharmD; and Jordi Rello, MD, PhD

- **Patient specific** (10 months); **scheduling**, including sequential quarterly prioritization (12 months) and **restriction** (12 months) of antimicrobials; and **mixing** (10 months).
- Results: Overall, 127 microbiologic VAP episodes were documented.
- **ESKAPE VAP increased significantly during scheduling** (AHI, 0.65) compared with patient-specific (AHI, 0.88) and mixing (AHI, 0.87) periods (RR 2.67 and 3.84, respectively).
- significant (P , .05) **increase of carbapenem-resistant A baumannii** during the **scheduling** period (**15.0%**) compared with the patient-specific (**2.4%**) and **mixing (0%)** periods.
- **ICU mortality** of resistant patients with ESKAPE VAP was **double** that of patients without ESKAPE VAP (relative risk, 2.25; 95% CI, 1.67-9.48).
- **30-day mechanical ventilation-free** days was **significantly increased** (5 days) in patients with **resistant ESKAPE VAP** .
- **Conclusions**: **Antibiotic strategies promoting diversity may prevent the emergence of resistance of ESKAPE organisms, improving use of health-care resources**



ITU VAP mixing last 12 months in England

- Blue: pip-tazo
- Red: 3G cephalosporins
- Green: carbapenem
- Orange: fluoroquinolones
- Grey: colistin

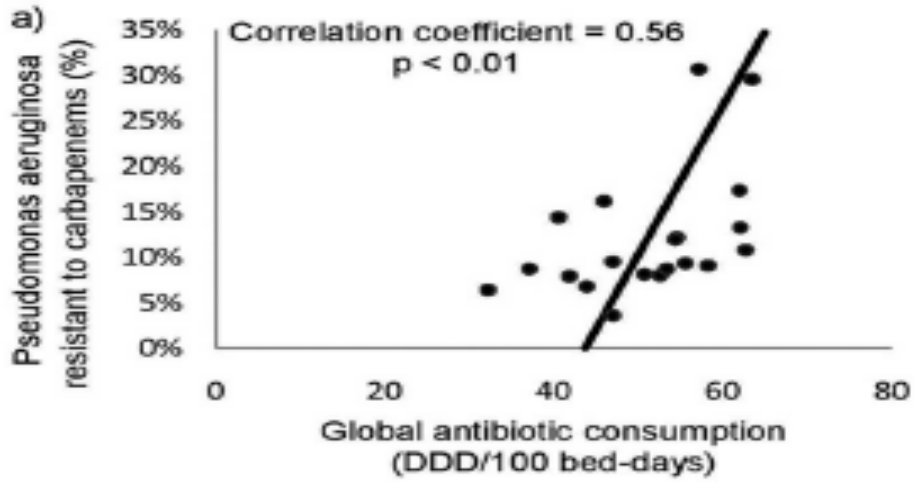
AAC Journals.ASM.org

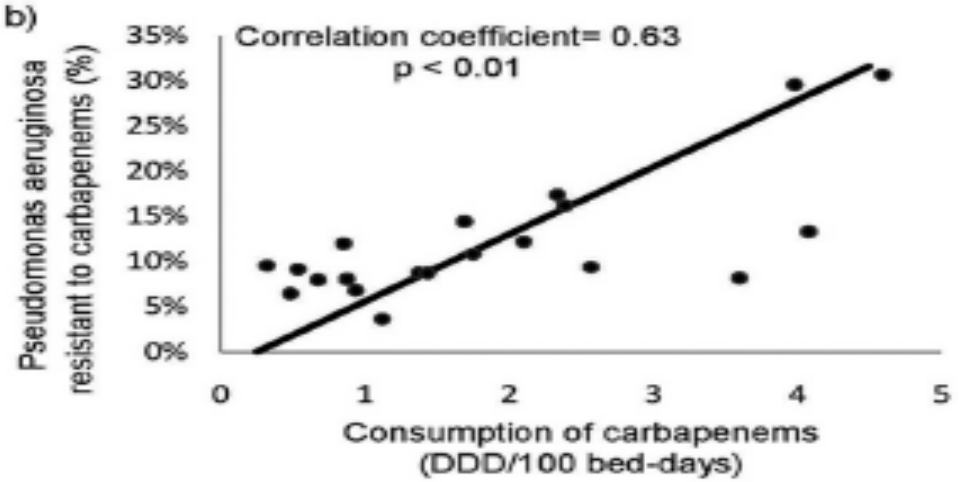
2013

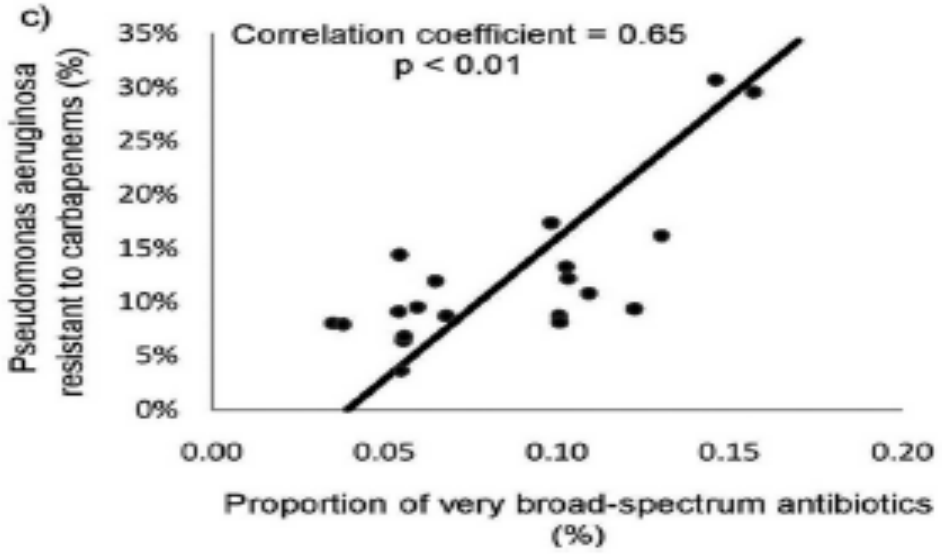
Impact of Antibiotic Use on Carbapenem Resistance in *Pseudomonas aeruginosa*: Is There a Role for Antibiotic Diversity?

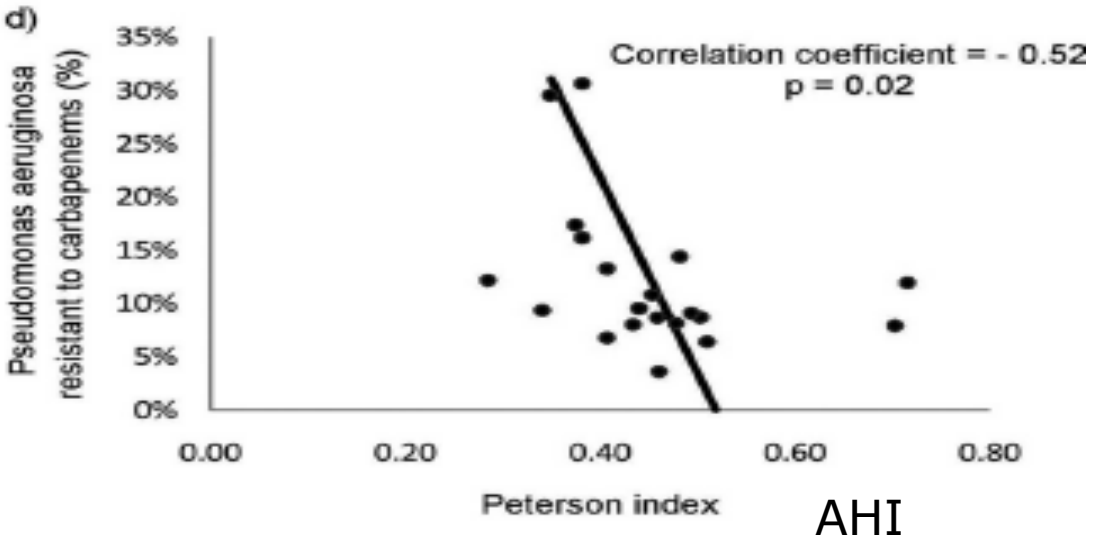
C. Plüss-Suard,[a,b] A. Pannatier,[c,d] A. Kronenberg,[e] K. Mühlemann,[e] G. Zanetti[f]

Service of Hospital Preventive Medicine, Lausanne University Hospital, Lausanne, Switzerland[a]; School of Pharmaceutical Science, University of Geneva and University of Lausanne, Geneva, Switzerland[b]; Service of Pharmacy, Lausanne University Hospital, Lausanne, Switzerland[c]; School of Pharmaceutical Science, University of Geneva and University of Lausanne, Geneva, Switzerland[d]; Institute for Infectious Diseases, University Hospital, Bern, Switzerland[e]; Service of Hospital Preventive Medicine and Service of Infectious Diseases, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland[f]









Swiss study looking at increasing Ps.aeruginosa resistance to carbapenems

AHI

OPEN ACCESS Freely available online

PLOS | PATHOGENS

Cycling Empirical Antibiotic Therapy in Hospitals: Meta-Analysis and Models

Pia Abel zur Wiesch[1,2]*, Roger Kouyos[1,3], Sören Abel[4], Wolfgang Viechtbauer[5], Sebastian Bonhoeffer[1]

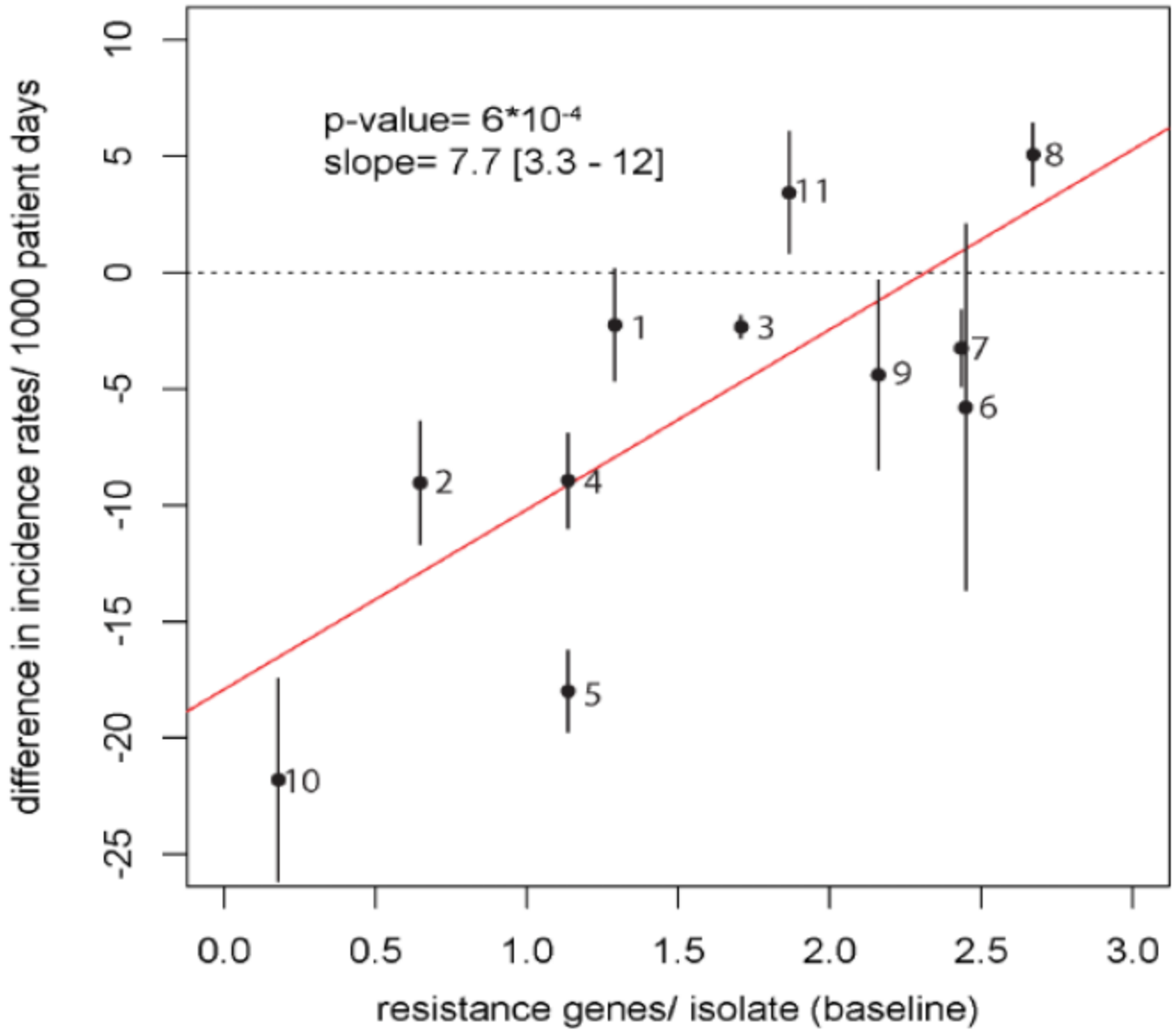
1 Institute of Integrative Biology, ETH Zurich, Zurich, Switzerland, 2 Division of Global Health Equity, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts, United States of America, 3 Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland, 4 Division of Infectious Diseases, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts, United States of America, 5 Department of Psychiatry and Psychology, School for Mental Health and Neuroscience, Faculty of Health, Medicine, and Life Sciences, Maastricht University, Maastricht, The Netherlands

- Compared cycling to standard practice (11 eligible studies from 46)
- 9 studies were in ITU, 1 at ward level and another hospital level
- Adjustable cycling / mixing is when empiric therapy is automatically changed when ineffective (clinical cycling)
- Adjustable cycling/mixing reduced incident rate / 1000 bed days of
  - Total infections by 4.95 (OR 9.43 – 0.48)
  - Resistant infections by 7.2 (OR 14.00 – 0.44)
- Strict cycling is detrimental

2014

http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004225

Where AMR is low, impact of clinical cycling largest



1) Bennett 2007

2) Chong 2013

3) Gerding 1991

4) Gruson 2000

5) Gruson 2003

6) Hedrick 2008

7) Kheder 2011_GIT

8) Kheder 2011_Urology

9) Nijssen 2010

10) Smith 2008

11) Toltzis 2002

Abel 2014 PLoS pathogens

Antibiotic Cycling and Antibiotic Mixing: Which One Best Mitigates Antibiotic Resistance?

Robert Eric Beardmore,*[1] Rafael Peña-Miller,[2] Fabio Gori,[1] and Jonathan Iredell[3]
[1]Biosciences University of Exeter, Devon, United Kingdom

Mol. Biol. Evol. 34(4):802–817 doi:10.1093/molbev/msw292 Advance Access publication January 17, 2017

known as "antibiotic cycling" and "antibiotic mixing." However, the accumulated data from clinical trials, now approaching 4 million patient days of treatment, is too variable for cycling or mixing to be deemed successful. The former implements the restriction and prioritization of different antibiotics at different times in hospitals in a manner said to "cycle" between them. In antibiotic mixing, appropriate antibiotics are allocated to patients but randomly. Mixing results in no correlation, in time or across patients, in the drugs used for treatment which is why theorists saw this as an optimal behavioral strategy. So while cycling and mixing were proposed as ways of controlling evolution, we show there is good reason why clinical datasets cannot choose between them: by re-examining the theoretical literature we show prior support for the theoretical optimality of mixing was misplaced. Our analysis is consistent with a pattern emerging in data: neither cycling or mixing is a priori better than the other at mitigating selection for antibiotic resistance in the clinic.

The effects of antibiotic cycling and mixing on antibiotic resistance in intensive care units: a cluster-randomised crossover trial

Pleun Joppe van Duijn, Walter Verbrugghe, Philippe Germaine Jorens, Fabian Spöhr, Dirk Schedler, Maria Deja, Andreas Rothbart, Djillali Annane, Christine Lawrence, Jean-Claude Nguyen Van, Benoit Misset, Matjaz Jereb, Katja Seme, Franc Šifrer, Viktorija Tomiç, Francisco Estevez, Jandira Carneiro, Stephan Harbarth, Marinus Johannes Cornelis Eijkemans, Marc Bonten, on behalf of the SATURN consortium

Lancet Infect Dis 2018; 18: 401–09

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January 24, 2018
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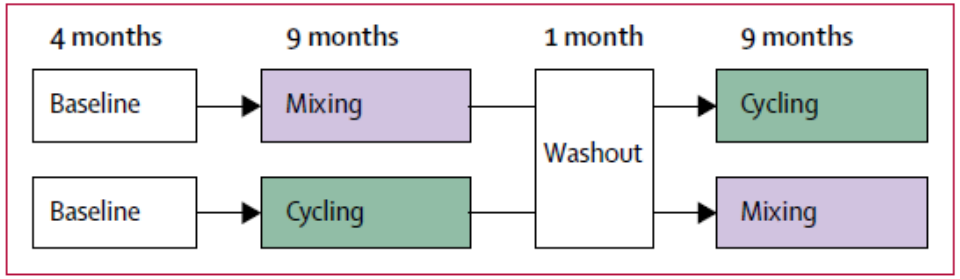
Empiric Gram negative cover

- 3rd or 4th generation cefalosporins
- Piperacillin-tazobactam
- Meropenem



- Cycling – order changed every 6 weeks
- Mixing – order changed with each patient

- De-escalation allowed
- Deviation only for allergy, known MDR colonisation, previous AB use

	Baseline	Cycling	Mixing	Mixing vs cycling*	Difference (95% CI)
Point-prevalence surveys	32	59†	70	..	..
Screened patients	462	745	853	..	..
Patients with antibiotic-resistant, Gram-negative bacteria‡	129 (28%)	168 (23%)	184 (22%)	0·64	1·0 (–3·1 to 5·1)
Enterobacteriaceae					
ESBL phenotype	97 (21%)	128 (17%)	127 (15%)	0·21	2·3 (–1·3 to 5·9)
ESBL genotype	58 (13%)	72 (10%)	68 (8%)	0·23	1·69 (–1·1 to 4·5)
CRE genotype	4 (1%)	7 (1%)	10 (1%)	0·65	–0·2 (–1·2 to 0·8)
Non-fermenters§					
Resistant to piperacillin–tazobactam or carbapenems	40 (9%)	61 (8%)	66 (8%)	0·74	0·5 (–2·2 to 3·1)
Pseudomonas aeruginosa					
Resistant to ceftazidime	5 (1%)	5 (1%)	2 (<1%)	0·19	0·4 (–0·2 to 1·1)
Resistant to piperacillin–tazobactam	20 (4%)	37 (5%)	25 (3%)	0·04	2·0 (0·1 to 4·0)
Resistant to carbapenems	29 (6%)	43 (6%)	53 (6%)	0·71	–0·4 (–2·8 to 1·9)
Acinetobacter spp					
Resistant to piperacillin–tazobactam	4 (1%)	7 (1%)	6 (1%)	0·60	0·2 (–0·7 to 1·1)
Resistant to carbapenems	1 (<1%)	6 (1%)	6 (1%)	0·81	0·1 (–0·8 to 1·0)

Data are n (%) unless otherwise stated. ESBL=extended-spectrum β-lactamase. CRE=carbapenem-resistant Enterobacteriaceae. ICU=intensive care unit. *χ^2 test for mixing *vs* cycling. †Number of point-prevalence surveys during cycling was lower than in mixing due to three missed surveys in one ICU and overall shorter total time-period of cycling compared with mixing. ‡Defined as carriage with Enterobacteriaceae bacteria harbouring ESBL genes, or with phenotypical resistance to piperacillin–tazobactam (Enterobacteriaceae, *Acinetobacter* spp or *P aeruginosa*) or carbapenems (*Acinetobacter* spp or *P aeruginosa*). §*P aeruginosa* and *Acinetobacter* spp.

Table 3: **Prevalence of antibiotic resistance at the patient level**

Cycling of antibiotic s for UTI prophylaxis

ELSEVIER

Médecine et maladies infectieuses 46 (2016) 294–299

Original article

Prevention of urinary tract infections by antibiotic cycling in spinal cord injury patients and low emergence of multidrug resistant bacteria

Prévention des infections urinaires par antibiothérapie cyclique chez les patients blessés médullaires et faible émergence de résistances

C. Poirier[a,*], A. Dinh[b], J. Salomon[b], N. Grall[c], A. Andremont[c], L. Bernard[a]

Had ≥4 UTIs in previous year.

Once weekly dose of different antibiotics based on their prior UTI sensitivities

- amoxicillin 3g
- cefixime 400mg
- fosfomycin 6g
- nitrofurantoin 300mg
- co-trimoxazole 1920mg

Table 2 Frequency of urinary traction infection, hospitalization, antibioticuse and multidrug resistant organisms (MDRO) organism colonization before and under weekly oral cycling antibiotics (WOCA).

	Prior WOCA	Under WOCA	*p*
Urinary tract infection (UTI) per patient per year:			
Cystitis	9.45	1.57	0.0001
Febrile UTI	5.25	0.18	0.0001
Hospitalization and antibiotic use:			
Hospitalizations per patient per year	0.86	0.02	0.002
Total hospital days per patient per year	5.37	0.16	0.001
Total days of curative antibiotic treatment per patient per year	92.83	34.5	<0.0001
MDR colonization:			
Percentage of positive urine sample cultures	86%	57%	<0.0001
MDRO-colonized patients	9	4	NS

Summary of heterogeneity

- Mixing and cycling is probably not an effective strategy to reduce AMR but only one RCT so far
- Need trials in primary care UTI to see if mixing can impact of AMR
- Small evidence for rotational antibiotics for preventing UTI
- Our empiric guidelines decrease diversity and probably drive resistance especially with broad spectrum agents, so stewardship is key.