CHALLENGES OF ANTIBIOTIC USE AND MITIGATION BY APPLYING HYGIENE

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Contents

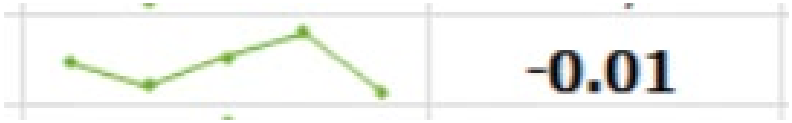
- Evolution of antibiotic use and antibiotic resistance
- Priority of infection prevention over therapy
- Elements of infection prevention in healthcare
- Role of biocieds in infection prevention
- Risk of biocide resistance
- Risk of biocide use promoting antibiotic resistance

Evolution of antibiotic use

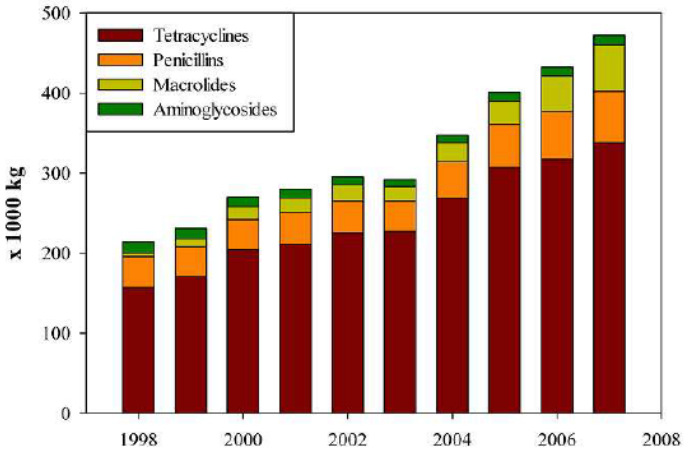
in humans + animals

ECDC report 2010-14

ECDC report 2013-17



in agriculture (NL 1997-2007)



ECDC reports antimicrobial consumption

Evidence of increasing antibiottic resistance gene abundance in archived soils since 1940, Environ Sci Technol 2010; 44: 580-587

Evolution of antibiotic use

Probable reasons

- Over-use of antibiotics in humans
  - Lack of knowledge
- Abuse of antibiotics in agriculture
  - Growth promotion
  - Plant and crop protection
- More invasive procedures
  - Increased need for prophylactic use
- Aging population
  - More infectious diseases need therapy

Consequence of this development

- Development of *Clostridioides difficile* infections (CDI)
  - 2016: 7 711 CDI cases reported by 20 EU countries, 74.6% healthcare-associated[1)]
  - Increasing number of deaths related to CDI[2)]
    UK 1999-2007
  - Antibiotic use being the main driver of this
    Example: Ciporfloxacin use and CDI[3)]
- Evidence for beneficial effect to stop CDI[4)]
  - Antimicrobial stewardship
  - Glove use
  - Disposable thermometers
  - Environmental disinfection

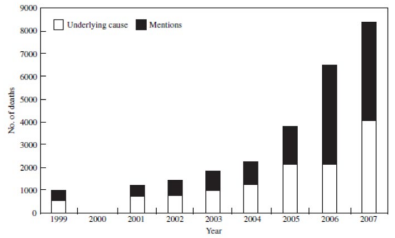
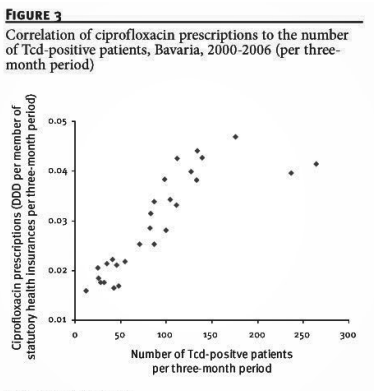


Figure 1 Number of deaths reported with *C. difficile* as underlying cause or mentioned 1993–2007. Data from the UK Office of National Statistics.



Add. Costs €12,500 extra 5.6 days in hospital per case

Leal et al., Infection Control & Hospital Epidemiology 2019, 1–9
doi:10.1017/ice.2019.178

1) ECDC Clostridium difficile infections -Annual Epidemiological Report for 2016
2) Pearson, J. Hosp Infect 2009; 73: 296-304
3) Borgmann et al. Eurosurveillance 15 No. 5, Feb 4th 2010
4) Hsu et al., American journal of gastroenterology 2010; 105 (11): 2327-239

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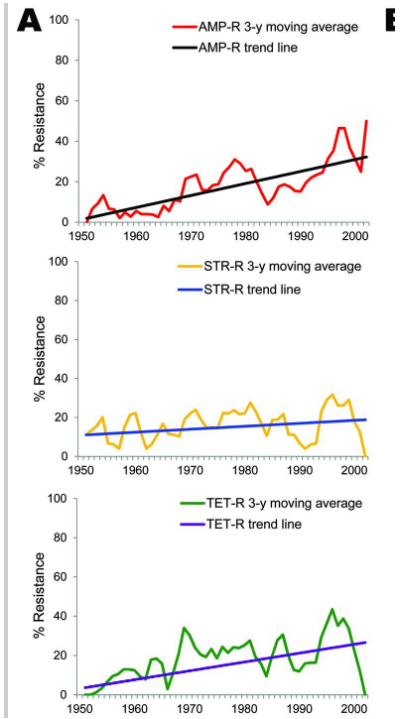
Evolution of antibiotic resistance

in humans + animals



in the environment

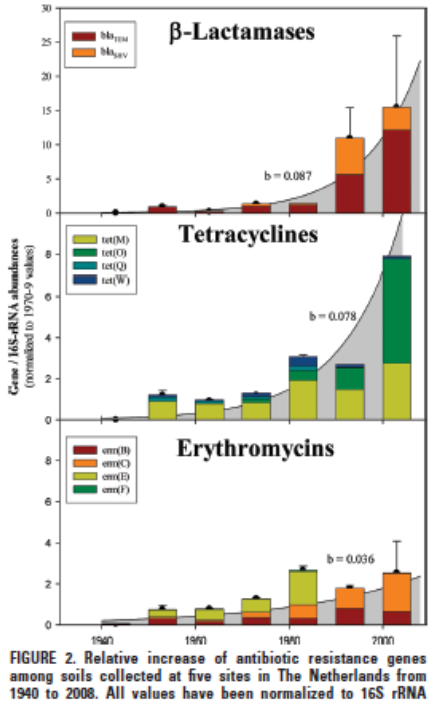


FIGURE 2. Relative increase of antibiotic resistance genes among soils collected at five sites in The Netherlands from 1940 to 2008. All values have been normalized to 16S rRNA

Tadesse et al, Antimicrobial Drug Resistance in *Escherichia coli* from Humans and Food Animals, United States, 1950–2002, Emeging Infect Dis 2012; 18: 741-749

Evicence of increasing antibiotzic resistance gene abundancesin archived soils since 1940, Environ Sci Technol 2010; 44: 580-587

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Evolution of antibiotic resistance

- Antibiotics
  - Found in 1928
  - In broad use since 1945
  - 1st resistance report: 1940 (acquired resistance, penicillinase)
  - Resistance of clinical relevance immediately after introduction
- Resistance to antibiotics was already out there
  - Antibiotics are “natural” substances
  - Microbes acquired resistance during evolution

Consequence of this development

- Infections, which can no more be treated
  - MRSA multi-resistant *Staphylococcus aureus*
  - VRE Vancomycin resistant Enterococci
  - MRGN multi-resistant gramnegative Bacteria
  - CDI Clostridioides difficile infection
- Some epidemiologists declared the “post-antibiotic era”
- 3 000 000 healthcare associated infections per year
- responsible for approximately 50 000 deaths

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1) The First European Communicable Disease Epidemiological Report, ECDC June 2007

Consequence of this development

- The frequency and rates of ascent and dissemination of antibiotic resistance in bacterial populations are anticipated to be directly related to the volume of antibiotic use[1)]

  => antibiotic stewardship

- Use (formerly) most powerful weapon against infections more carefully and targeted

- Focus on infection prevention rather than treatment
  - "The goal of controlling antimicrobial resistance can only be achieved by combining strong infection prevention and control and the prudent use of antimicrobials."[2)]

1) Anderson & Levin, CurrentOpinion in Microbiology 1999; 2: 483-493

2) Commission Notice EU Guidelines for the prudent use of antimicrobials in human health (2017/C 212/01)

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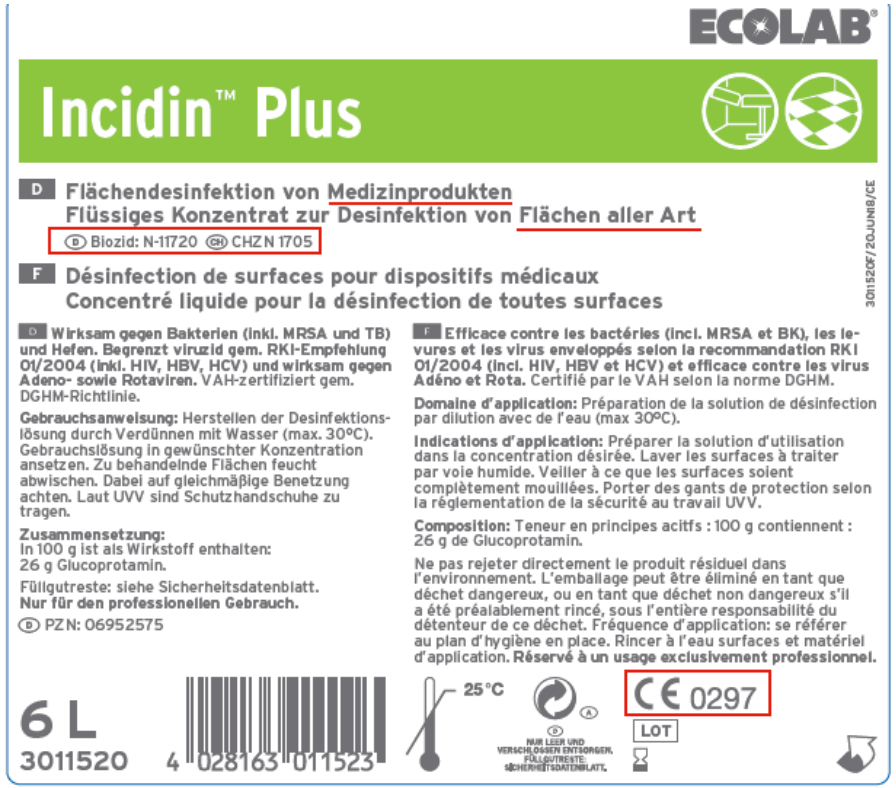
Elements of infection prevention in healthcare

- surveillance
- Isolation of cases
- Barrier management
  - Personal protective equipment, probe covers, patient drapes, ….
- Hygienic design of environment and devices
- Disinfection + antisepsis

Elements of infection prevention in healthcare

- Disinfection + antisepsis
  - Hands — biocides
  - Patient environment (surfaces) — biocides / medical devices
  - Medical instruments — medical devices
  - Pre-invasive skin antisepsis — medicinal products



Role of biocides in infection prevention

Hand disinfection reduces infection rates

- Overwhelming scientific evidence published by WHO

  WHO Guideliens on Hand Hygiene in Health Care: a Summa0ry, https://www.who.int/gpsc/5may/tools/9789241597906/en/

- The preferred measure:
  - alcohol based hand disinfection
  - Unless hands are visibly soiled
  - Unless contaminated with spores

Year	Authors	Hospital setting	Major results	Duration of follow-up
1977	Casewell & Phillips[88]	Adult ICU	Significant reduction in the percentage of patients colonized or infected by Klebsiella spp.	2 years
1989	Conly et al.[41]	Adult ICU	Significant reduction in HCAI rates immediately after hand hygiene promotion (from 33% to 12% and from 33% to 10%, after two intervention periods 4 years apart, respectively)	6 years
1990	Simmons et al.[117]	Adult ICU	No impact on HCAI rates (no statistically significant improvement of hand hygiene adherence)	11 months
1992	Doebbeling et al.[119]	Adult ICUs	Significant difference between rates of HCAI using two different hand hygiene agents	8 months
1994	Webster et al.[74]	NICU	Elimination of MRSA when combined with multiple other infection control measures. Reduction of vancomycin use. Significant reduction of nosocomial bacteremia (from 2.6% to 1.1%) using triclosan compared to chlorhexidine for handwashing	9 months
1995	Zafar et al.[87]	Newborn nursery	Control of a MRSA outbreak using a triclosan preparation for handwashing, in addition to other infection control measures	3.5 years
2000	Larson et al.[119]	MICU/NICU	Significant (85%) relative reduction of the vancomycin-resistant enterococci (VRE) rate in the intervention hospital; statistically insignificant (44%) relative reduction in control hospital; no significant change in MRSA	8 months
2000	Pittet et al.[75,120]	Hospital-wide	Significant reduction in the annual overall prevalence of HCAI (42%) and MRSA cross-transmission rates (87%). Active surveillance cultures and contact precautions were implemented during same time period. A follow-up study showed continuous increase in handrub use, stable HCAI rates and cost savings derived from the strategy.	8 years
2003	Hilburn et al.[121]	Orthopaedic surgical unit	36% decrease of urinary tract infection and SSI rates (from 8.2% to 5.3%)	10 months
2004	MacDonald et al.[77]	Hospital-wide	Significant reduction in hospital-acquired MRSA cases (from 1.9% to 0.9%)	1 year
2004	Swoboda et al.[122]	Adult intermediate care unit	Reduction in HCAI rates (not statistically significant)	2.5 months
2004	Lam et al.[123]	NICU	Reduction (not statistically significant) in HCAI rates (from 11.3/1000 patient-days to 6.2/1000 patient-days)	6 months
2004	Won et al.[124]	NICU	Significant reduction in HCAI rates (from 15.1/1000 patient-days to 10.7/1000 patient-days), in particular of respiratory infections	2 years
2005	Zerr et al.[125]	Hospital-wide	Significant reduction in hospital-associated rotavirus infections	4 years
2005	Rosenthal et al.[126]	Adult ICUs	Significant reduction in HCAI rates (from 47.5/1000 patient-days to 27.9/1000 patient-days)	21 months
2005	Johnson et al.[127]	Hospital-wide	Significant reduction (57%) in MRSA bacteraemia	36 months
2007	Thi Anh Thu et al.[128]	Neurosurgery	Reduction (54%, NS) of overall incidence of SSI. Significant reduction (100%) of superficial SSI; significantly lower SSI incidence in intervention ward compared with control ward	2 years
2007	Pessoa-Silva et al.[111]	Neonatal unit	Reduction of overall HCAI rates (from 11 to 8.2 infections per 1000 patient-days) and 60% decrease of risk of HCAI in very low birth weight neonates (from 15.5 to 8.8 episodes/1000 patient-days)	27 months
2008	Rupp et al.[112]	ICU	No impact on device-associated infection and infections due to multidrug-resistant pathogens	2 years
2008	Grayson et al.[129]	1) 6 pilot hospitals 2) all public hospitals in Victoria (Australia)	1) Significant reduction of MRSA bacteraemia (from 0.05/100 patient-discharges to 0.02/100 patient-discharges per month) and of clinical MRSA isolates 2) Significant reduction of MRSA bacteraemia (from 0.03/100 patient-discharges to 0.01/100 patient-discharges per month) and of clinical MRSA isolates	1) 2 years 2) 1 year

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Role of biocides in infection prevention

Hand disinfection reduces infection rates

The risk of non-compliance in hand hygiene

- Simulation study: 1 Mio patient-HCW-patient contacts without hand disinfection
- Results in
  - 42 MRSA infections (1st patient unknown MRSA status)
  - 980 MRSA infections (1st patient known MRSA carrier)
- Cost of one non-compliant event
  - 1.98 $ (1st patient unknown MRSA status)
  - 52.53 $ (1st patient known MRSA carrier)

Cummings, Infect Control Hosp Epidemiol 2010;31:357–364

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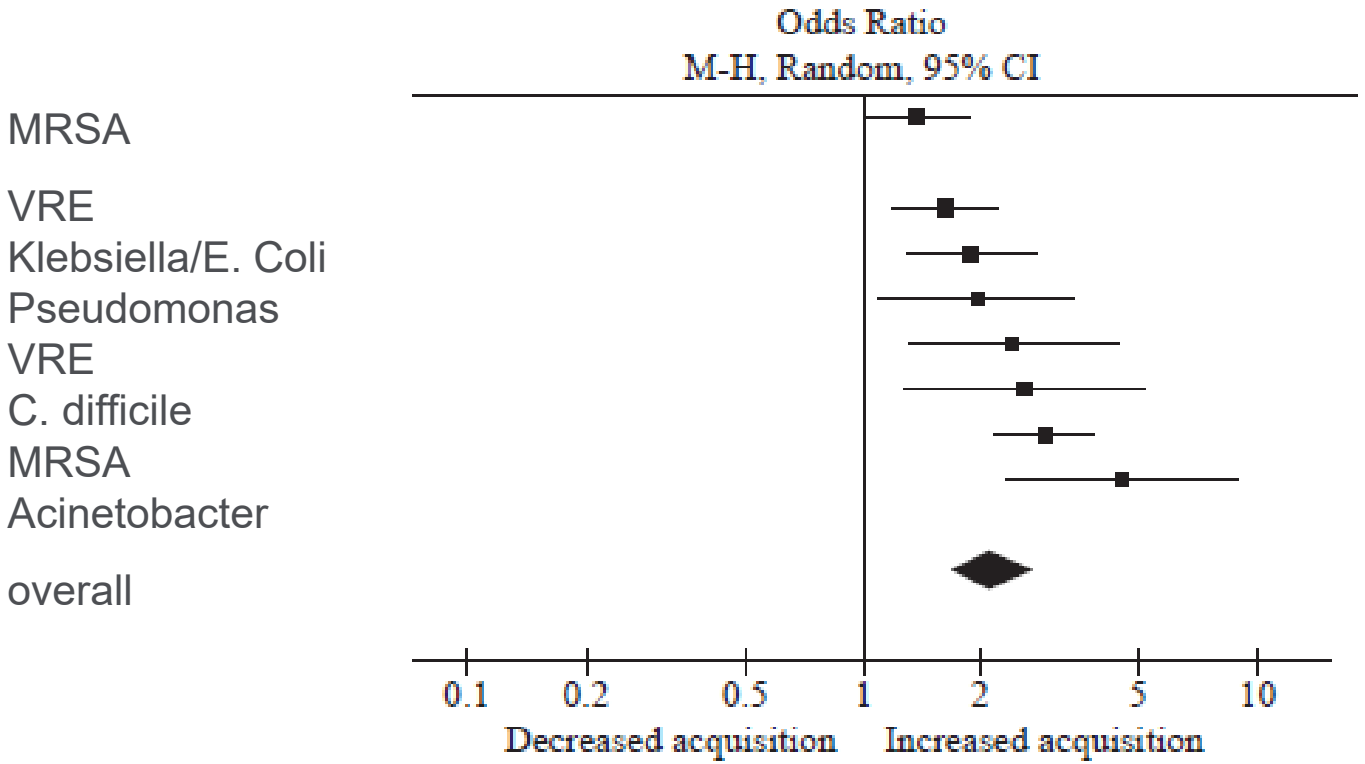
Role of biocides in infection prevention

Environmental disinfection reduces infection rates

Risk of organism transmission from prior room occupants: review and meta-analysis



Environmental surfaces play a significant role in pathogen transmission.

Mitchell et al., J Hops Infect 2015; 91: 211-217

Role of biocides in infection prevention

Environmental disinfection reduces infection rates

- Strong interrupted time series study with control group
- Replacing mere cleaning of high touch objects in patient rooms by disinfection
  - Significantly reduced the rate of VRE
  - Significantly reduced rates of CDI and MRSA infection, when disinfection compliance was ≥80%

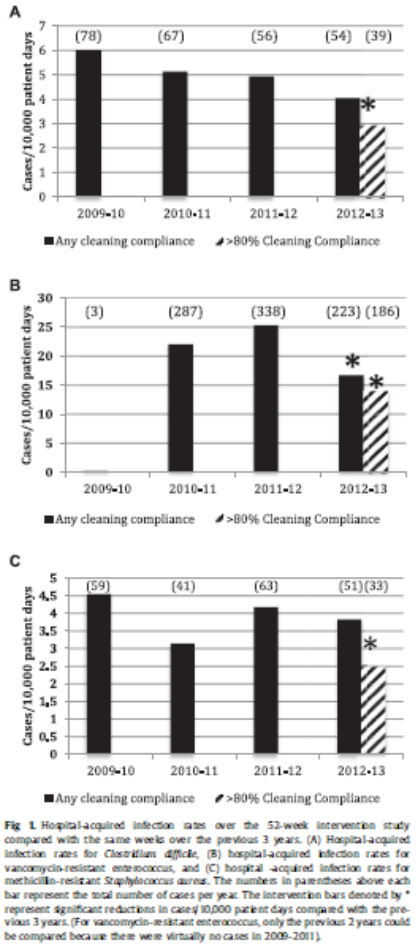


Fig 1. Hospital-acquired infection rates over the 52-week intervention study compared with the same weeks over the previous 3 years. (A) Hospital-acquired infection rates for *Clostridium difficile*, (B) hospital-acquired infection rates for vancomycin-resistant enterococcus, and (C) hospital -acquired infection rates for methicillin-resistant *Staphylococcus aureus*. The numbers in parentheses above each bar represent the total number of cases per year. The intervention bars denoted by * represent significant reductions in cases/ 10,000 patient days compared with the previous 3 years. (For vancomycin-resistant enterococcus, only the previous 2 years could be compared because there were virtually no cases in 2009-2011).

Alfa et al. AJIC 2014 doi.org/10.1016/j.ajic.2014.10.016

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Role of biocides in infection prevention

Environmental disinfection reduces infection rates

„The value of objectively monitoring environmental cleaning in healthcare settings is becoming increasingly recognized…“[1)]

- Application of biocides must be accompanied by
  - Appropriate use instructions
  - Training tools and systems
  - Compliance monitoring
  - Feedback

Carling, Am J Unfect Control 2013; 41: S20-S25

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Role of biocides in infection prevention

Combination of surface + hand disinfection most effective

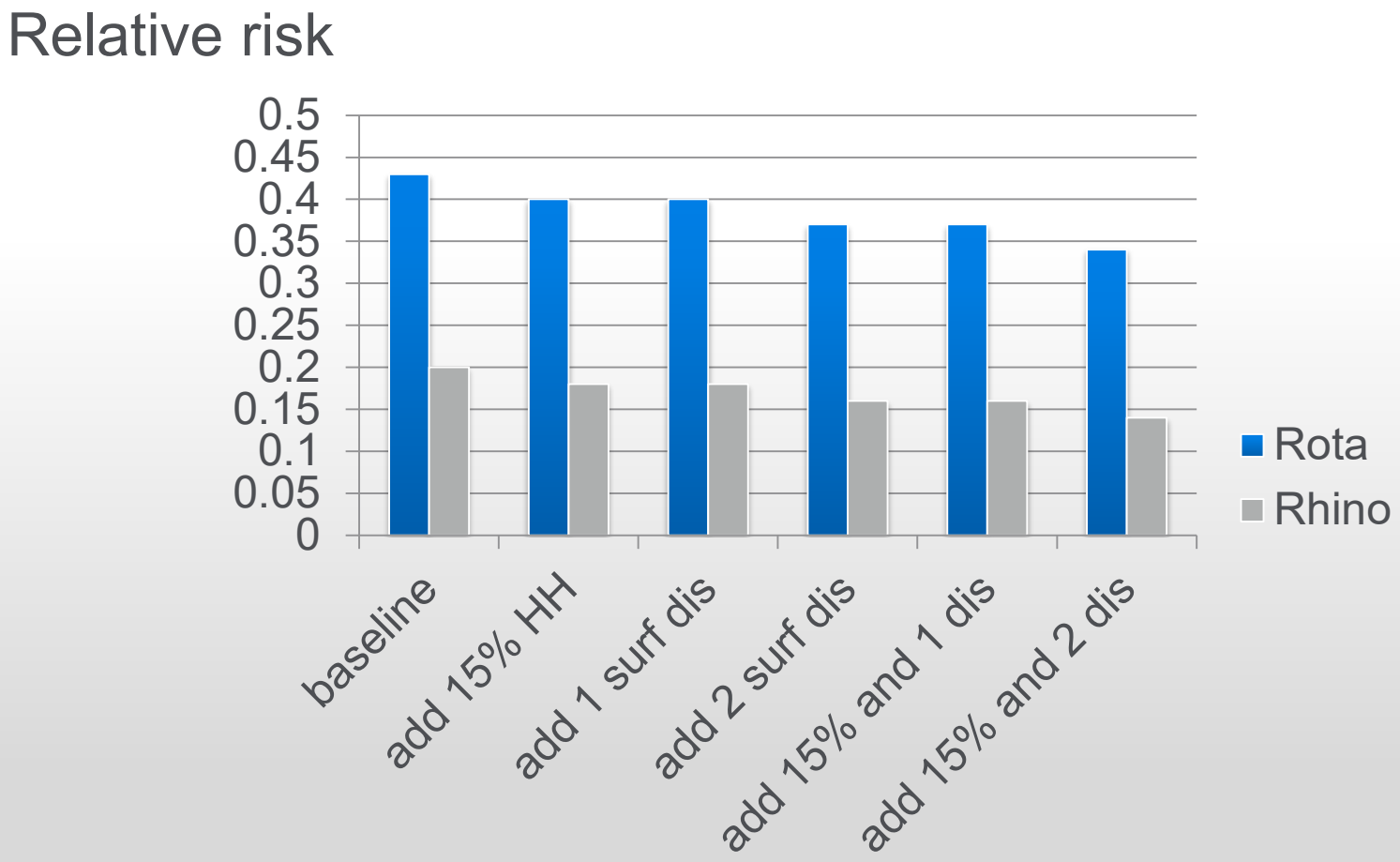
Mathematical model to estimate virus infection risk reduction in healthcare

- 15% hand hygiene increase or 1 surface disinfection event yielded similar infection risk reductions.
- 15% hand hygiene increase and 2 cleanings decreased infection risk by 20.93%-47.55%.
- Risk reduction for greater hand hygiene decreased as baseline compliance increased.

Wilson et al., AM J Infect Control 2019, https://doi.org/10.1016/j.ajic.2019.05.023

Role of biocides in infection prevention

Combination of surface + hand disinfection most effective



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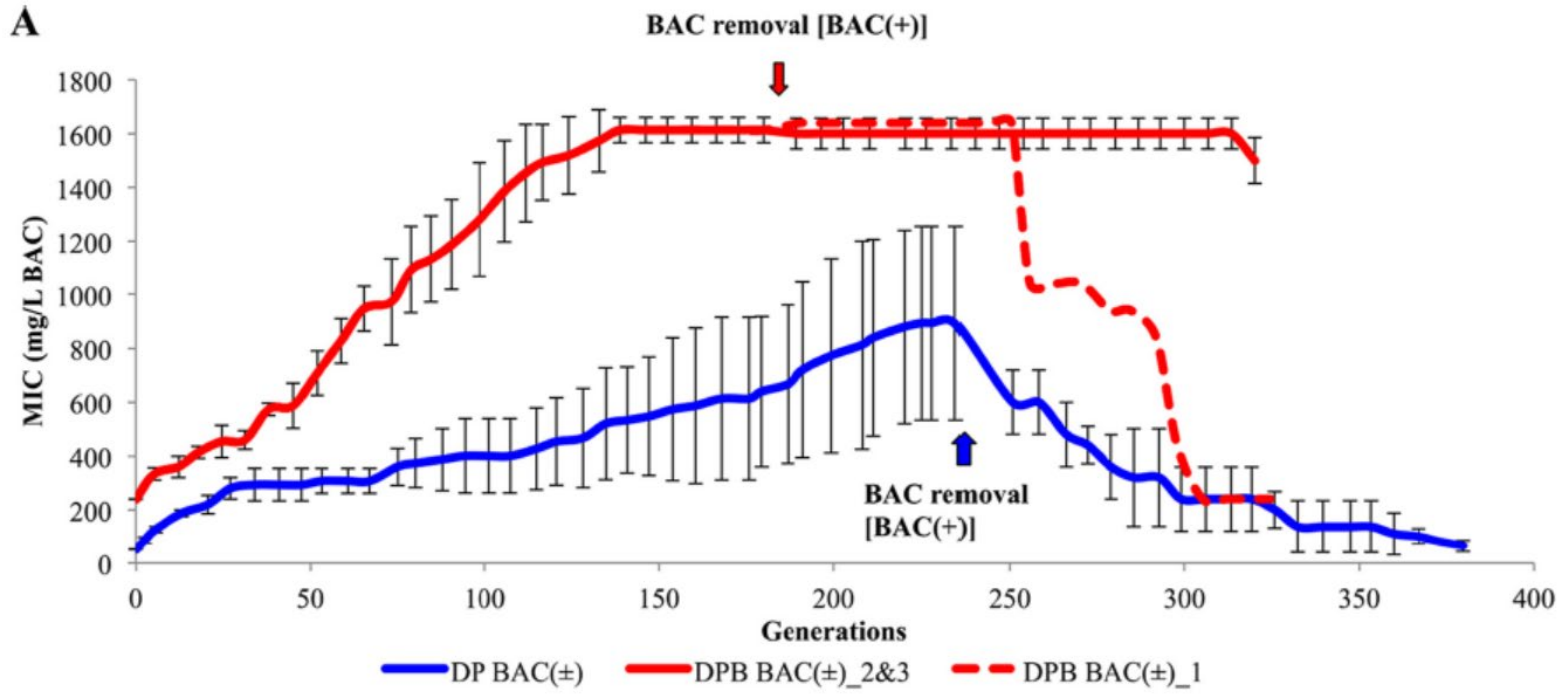
Wilson et al., AM J Infect Control 2019, https://doi.org/10.1016/j.ajic.2019.05.023

Does more frequent use of biocides promote biocide resistance?

- Long term exposure to subinhibitory concentrations BAC
  - Pre-adaptastion to 50 ppm BAC in a fed batch reactorfor 3 years!



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Kim et al., Appl. Environm. Microbiol. 2018; 84 (12): e00197-18

Does more frequent use of biocides promote biocide resistance?

Long term exposure to subinhibitory concentrations

Dramatic?
Relevant?

No!

- MIC does not represent practice conditions
  - high organic burden
- Such long-term exposure under conditions of growth does not occur in practice
  - Max. concentration in waste water of indirect discharge facilities using such disinfectants:
    - <1.5 ppm BAC and <5 ppm overall QAC[1)]
    - One single extreme value in a hospital: 6 ppm[2)]
- Start of reversion after 300 + generations?

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1) Martínes-Carball et al, Environmental Pollution 2007; 145: 489-496
2) Kümmerer et al, Journal of Chromatography A 1997; 774: 281-286

Does more frequent use of biocides promote biocide resistance?

Effects observed in the laboratory do not occur in real life

- effects of a QAC-containing domestic cleaning fluid on the population dynamics and antimicrobial susceptibility of domestic sink drain biofilm communities
- fully characterized drain microcosm was exposed to short-term (12 days) and long-term (3 months) dosing with a QAC-containing domestic detergent
- Although repeated QAC exposure of drain isolates in pure culture results in susceptibility change in some test bacteria, such changes do not necessarily occur within complex communities.

McBain et al. Appl. Environm. Microbiol. 2004; 70: 3449-3556

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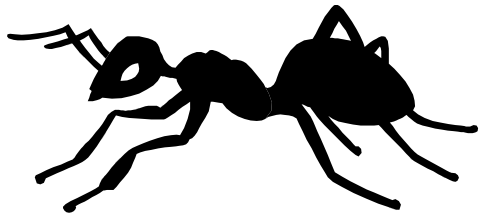
Does more frequent use of biocides promote biocide resistance?

Effects observed in the laboratory do not occur in real life

- Ants disinfect their houses by including conifera woods
  - Using biocides is “natural”
  - Microbes have **not** acquired resistance during evolution



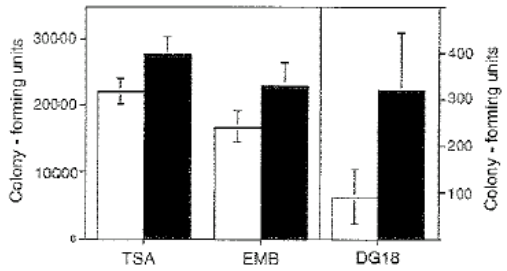


Figure 1 Mean (± SE) number of colony-forming units of bacteria and fungi per 10^{-4} gram of nest material, for nests containing resin (white bars) and resin-free nests (black bars). Tryptic Soy Agar (TSA) is a standard nutritive medium for bacteria, Eosin Methylene Blue agar (EMB) is specific for gram-negative bacteria, and Dichloran Glycerol (18) agar (DG18) is specific for xerophilic fungi.

Evidence for collective medication in ants Christe et al. Ecology Letters 6 (2003) 19-22

Does more stringent hygiene promote antibiotic resistance?

- „…increased confinement and cleaning is associated with a loss of diversity…“[1)]
- „…the loss of microbial diversity correlates with increase in (antibiotic) resistance…“
  - Determined as availability of resistance genes in the environment of healtcare and cleanroom (space craft assemby) settings
- The same was not observed in food manufacturing
  - The BIOHYPO project:
    No correlation between biocide and antibiotic susceptibility.[2)]
  - So far, data from the BIOHYPO project do not allow for the indication of any risk of clinically significant antibiotic resistance development following the use of biocides[3)]

1) Mahnert et al., Nature Communications, DOI: 10.1038/s41467-019-08864-0
2) http://cordis.europa.eu/result/rcn/89974_de.html
3) Oggioni et al., Expert Rev. Anti Infect Ther. 2013; 11: 363-366

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Does biocide use promote antibiotic resistance?

- The increased rate of resistance genes is probably not due to biocide use
  - Was not demonstrated in food settings, which are equally confined and disinfected
- The increased rate of resistance genes in healthcare settings may be due to antibiotic use
- The cleanroom situation needs further investigation

Conclusions (1)

- Infection risks must be weighed against the (potential and unknown) effects of reducing microbial diversity
  - In proven cases the benefit in infection prevention outweighs by far the risk of developing biocide resistance or promoting antibiotic resistance
  - Proven cases: hand disinfection, disinfection of high touch surfaces
- Biocides must be used according to use instructions to achieve infection prevention
  - Compliance and correct use must be supervised and instructed
  - Biocides must **not** be used to „disinfect dirt“ – appropriate pre-treatment, if needed

Conclusions (2)

- Biocides must be used targeted to risk areas and places to achieve infection prevention
- Appropriate biocide use does not promote biocide resistance
- Appropriate biocide use does not promote antibiotic resistance
- Biocides play a crucial role in infection prevention in the „post-antibiotic era“

THANK YOU

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