Hospital Vila Franca de Xira

HOSPITAL DA LUZ

8º SIMPÓSIO DE CONTROLO DE INFEÇÃO

IACS 2015: GLOBALIZAÇÃO E EPIDEMIAS - OLHANDO PARA 2014

23 de abril 2015 | Auditório do Hospital da Luz

João Gonçalves Pereira
ICU director
Vila Franca Xira Hospital

Antibioterapia

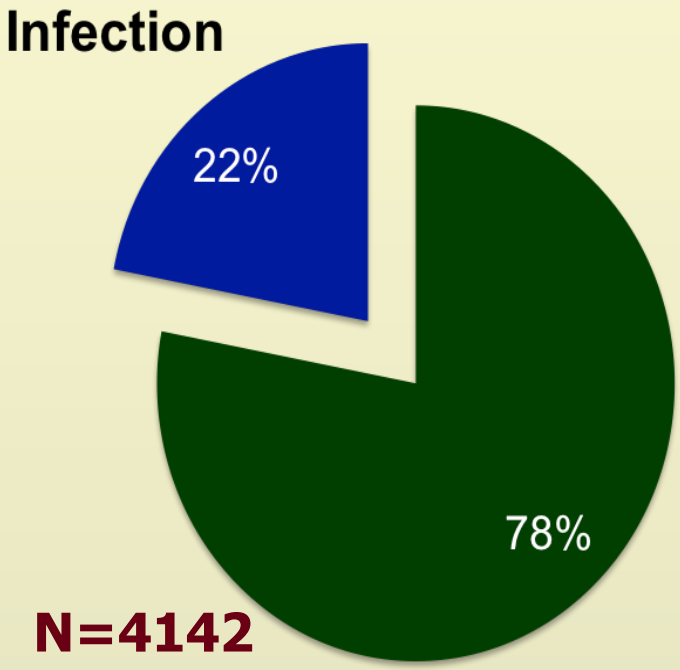
Utilização de antibióticos e risco de infeção

"You're only given a little spark of madness. You mustn't lose it."

Robin Williams

Infection Incidence

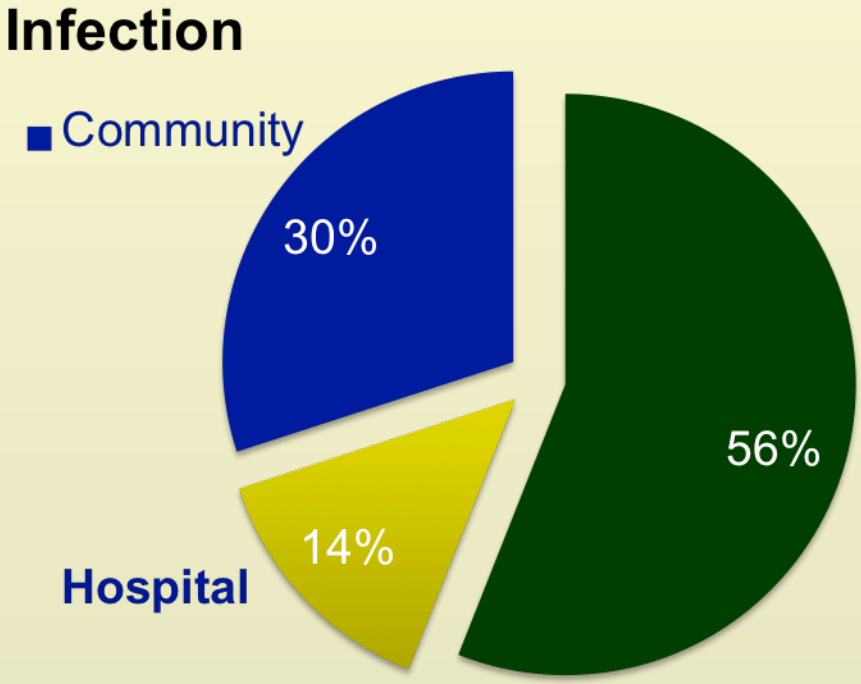
SAC UCI



N=4142

Cardoso, Crit Care, 2010, 14: R83

INFAUCI



N=3572

Gonçalves-Pereira, Clin Microbiol Infect 2014, 12: 1308

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Impact of Infection on the mortality

SAC UCI	No infection	Infection	
ICU mortality	23%	30%	<0.001
Hospital mortality	32%	38%	0.003

INFAUCI	No infection	Infection	
ICU mortality	19%	27%	<0.001
Hospital mortality	26%	38%	<0.001

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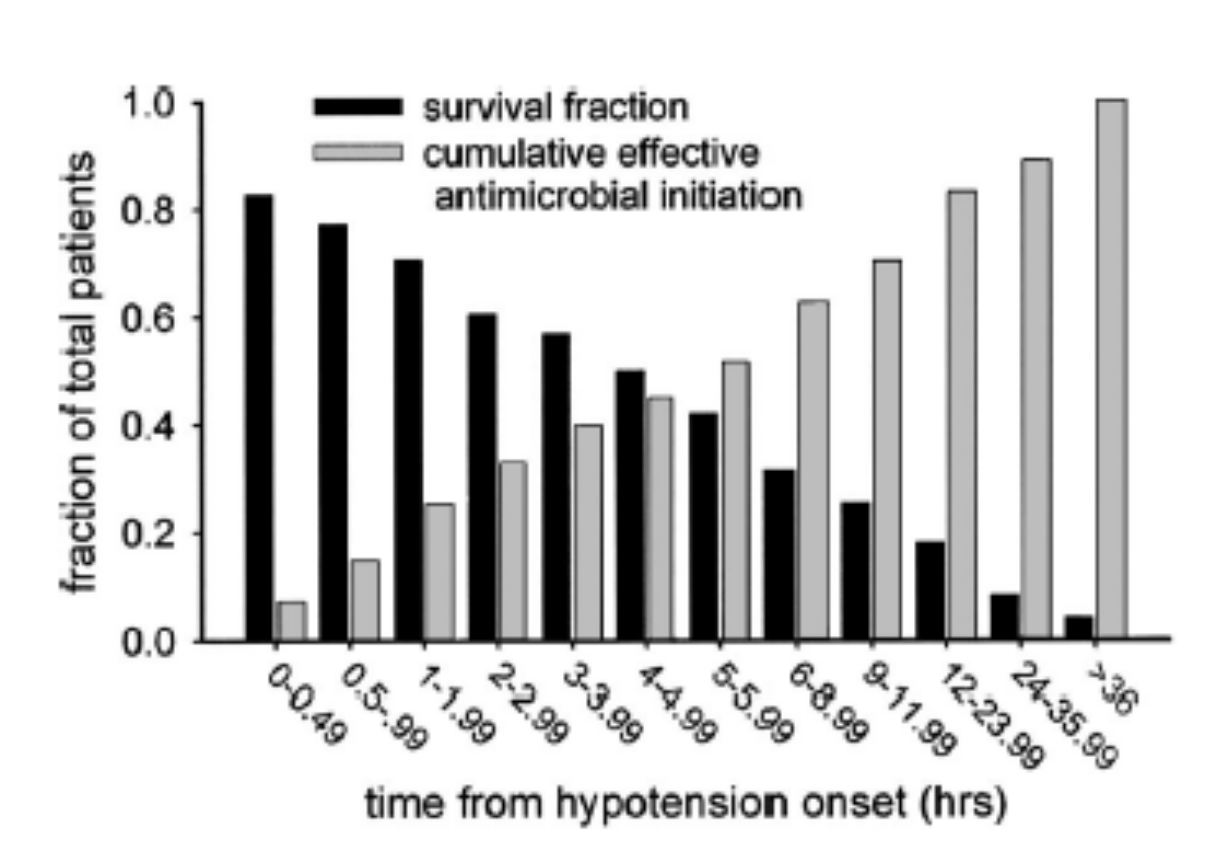
Infection and antibiotics

- AB delay → poor outcome



Only 50% receive ab until 6h after admission

Kumar CCM 2006;34:1589

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Antibiotics

one sword, two edges

Antibiotics

- Antibiotics help cure infections by decreasing the bacterial population to a level that the human immune system can handle

Early antibiotics should be good...

Author	n	Setting	Median time (mins)	Odds Ratio for death
Gaieski Crit Care Med 2010; 38:1045-53	261	ED, USA (Shock)	119	0.30 (first hour vs all times)
Daniels Emerg Med J 2010; doi: 10.1136	567	Whole hospital, UK	121	0.62 (first hour vs all times)
Kumar Crit Care Med 2006; 34(6): 1589-1596	2154	ED, Canada (Shock)	360	0.59 (first hour vs second hour)
Appelboam Critical Care 2010; 14(Suppl 1): 50	375	Whole hospital, UK	240	0.74 (first 3 hours vs delayed)
Levy Crit Care Med 2010; 38 (2): 1-8	15022	Multi-centre		0.86 (first 3 hours vs delayed)

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Documented Infections

	Stratification of sepsis			Positive Microbiology	Appropriate Antibiotic
	Sepsis	Severe Sepsis	Septic shock		
Total	312 (19.0%)	478 (29.1%)	850 (51.8%)	48.3%	74.4%
Pneumonia (N=745)	21.1%	34.0%	45.0%	39.7%	75.5%
Tracheobronchitis (N=102)	51.0%	30.4%	18.6%	44.1%	79.1%
Intra-Abdominal (N=436)	11.5%	22.9%	65.6%	47.9%	67.0%
Endovascular (N=101)	6.9%	26.7%	66.3%	77.2%	74.0%
Skin and soft tissue (N=93)	19.4%	28.0%	52.7%	60.2%	74.1%
Urological (N=92)	9.8%	18.5%	71.7%	70.7%	89.8%
Neurological (N=43)	32.6%	39.5%	27.9%	53.5%	89.5%
Other (N=28)	17.9%	25.0%	57.1%	42.9%	92.3%

Gonçalves-Pereira, Clin Microbiol Infect 2014, 12: 1308

SAC UCI Positive microbiology 40.7%

Cardoso, Crit Care, 2010, 14: R83

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Documented Infections

SAC UCI

Mortality and Time of Antibiotic Therapy (<3h/≥3h)

	N	<3h	≥ 3h	OR	95% CI	P
Total	707	**24.2%**	**32.6%**	**1.52**	1.05-2.20	**0.026**
Documented Infection	288	**24.3%**	**37.9%**	**1.90**	1.04-3.45	**0.035**
Presumed	419	**24.1%**	**28.7%**	**1.27**	0.79-2.04	**0,32**

Gonçalves-Pereira, ATS 2011 P B104

Patients who are lately found to be non infected are usually excluded from analysis…

Less AB
Lower mortality and LOS

Weiss AJRCCM 2011;164:680

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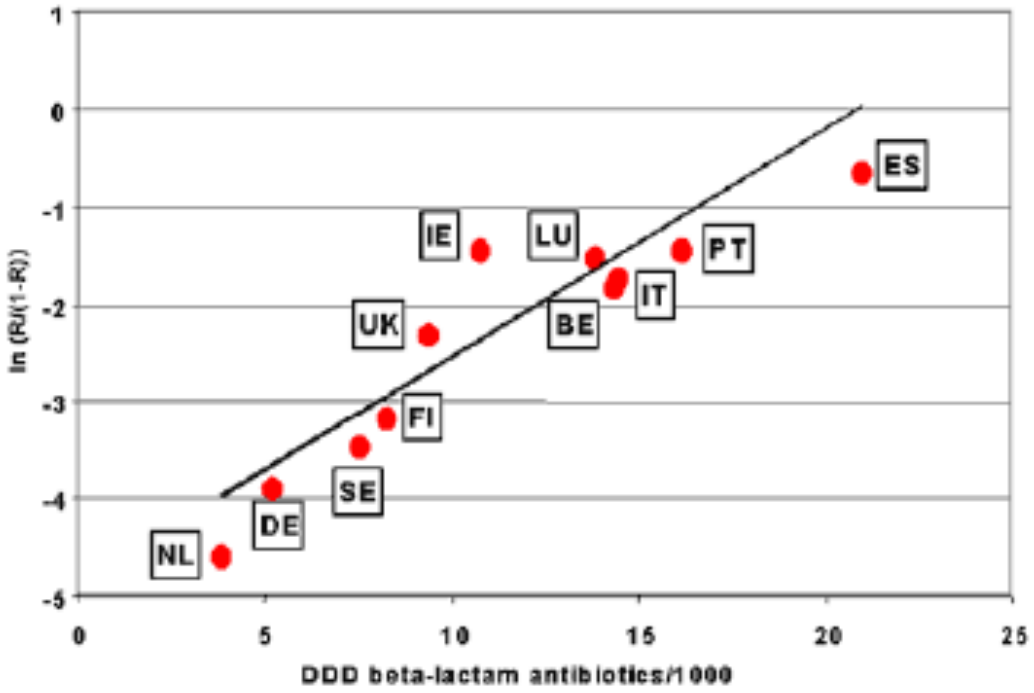
Correlation between resistance and antibiotic use

Overuse is also the problem …



Risk of resistance to β-lactams among invasive isolates of *Streptoccus pneumoniae* regressed against outpatient sales of beta-lactam antibiotics in 11 European countries

- resistance data are from 1998 to 1999; antibiotic sales data 1997.
- DDD = defined daily doses

Bronzwaer SL, Cars O, et al. Emerg Infect Dis 2002 Mar;8(3):278-82

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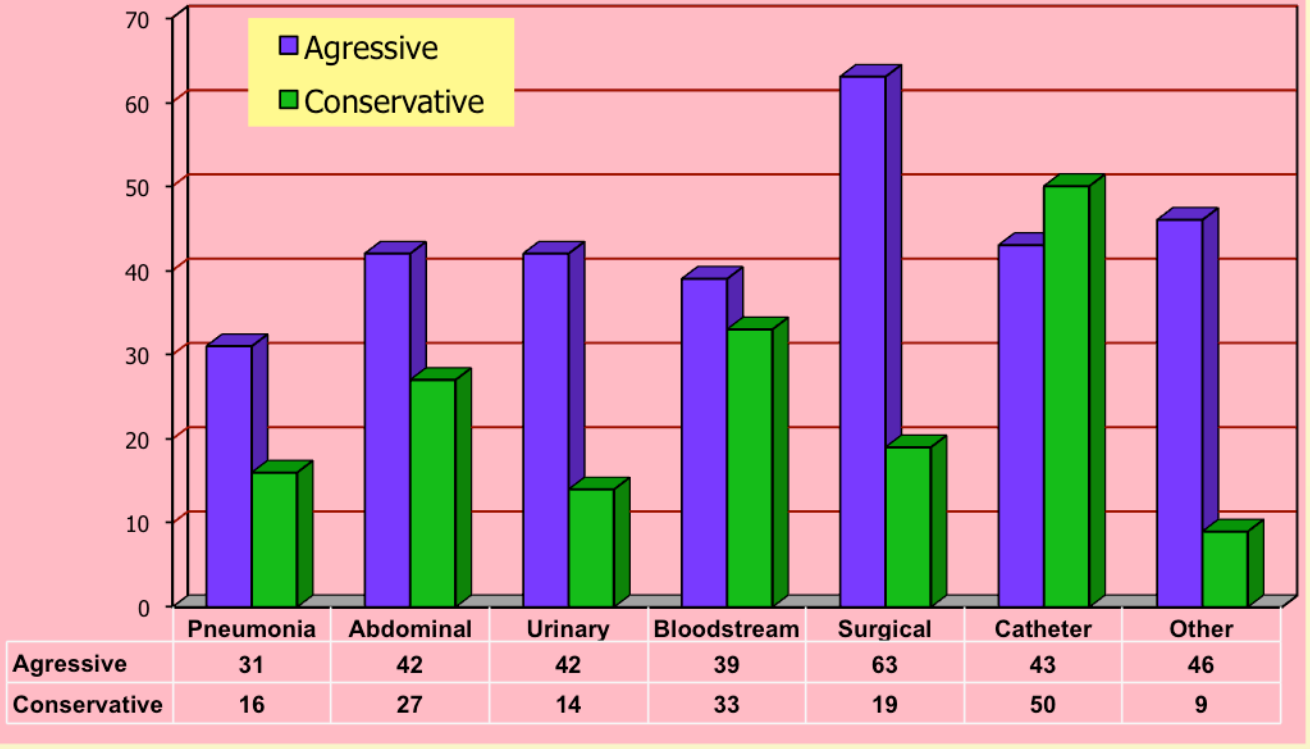
Time of antibiotics and Mortality



	Pneumonia	Abdominal	Urinary	Bloodstream	Surgical	Catheter	Other
Agressive	31	42	42	39	63	43	46
Conservative	16	27	14	33	19	50	9

- ✓ Before-after study
- ✓ Surgical patients

- ◆ **Mortality 13% vs. 27%**; p=0.015; AOR 2.5 (1.5-4.0)
- ◆ LOS 12.5 vs 17.7 days (p=0.008)

Patients with shock could have antibiotics started immediately after cultures

Hranjec, Lancet Inf Dis 2012; 12:774

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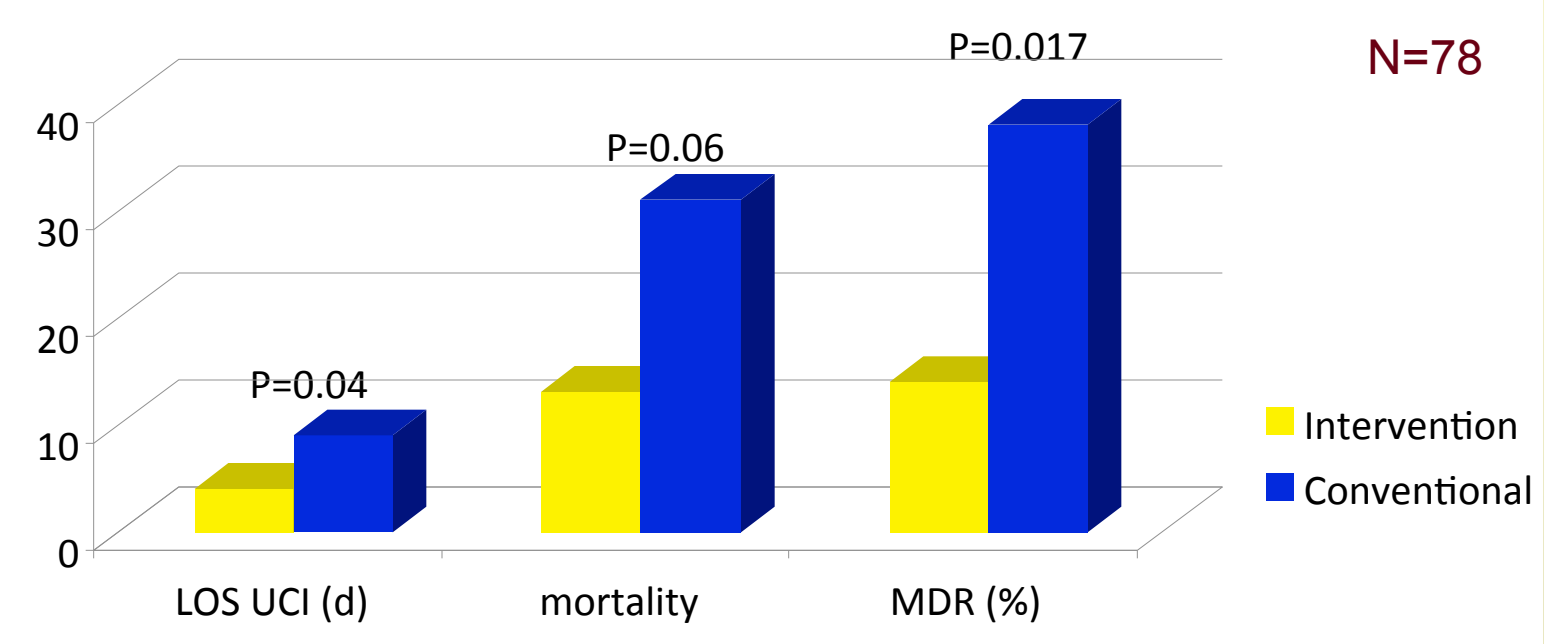
Short-course Empiric Antibiotic Therapy for Patients with Pulmonary Infiltrates in the Intensive Care Unit

A Proposed Solution for Indiscriminate Antibiotic Prescription

NINA SINGH, PAUL ROGERS, CHARLES W. ATWOOD, MARILYN M. WAGENER, and VICTOR L. YU

Low suspition of VAP (CPIS≤6)
Antibiotics (median) intervention 3d vs. standard 9.8d



Superinfection 14% vs. 38% p=0.017

Singh AJRCCM 2000;162:505

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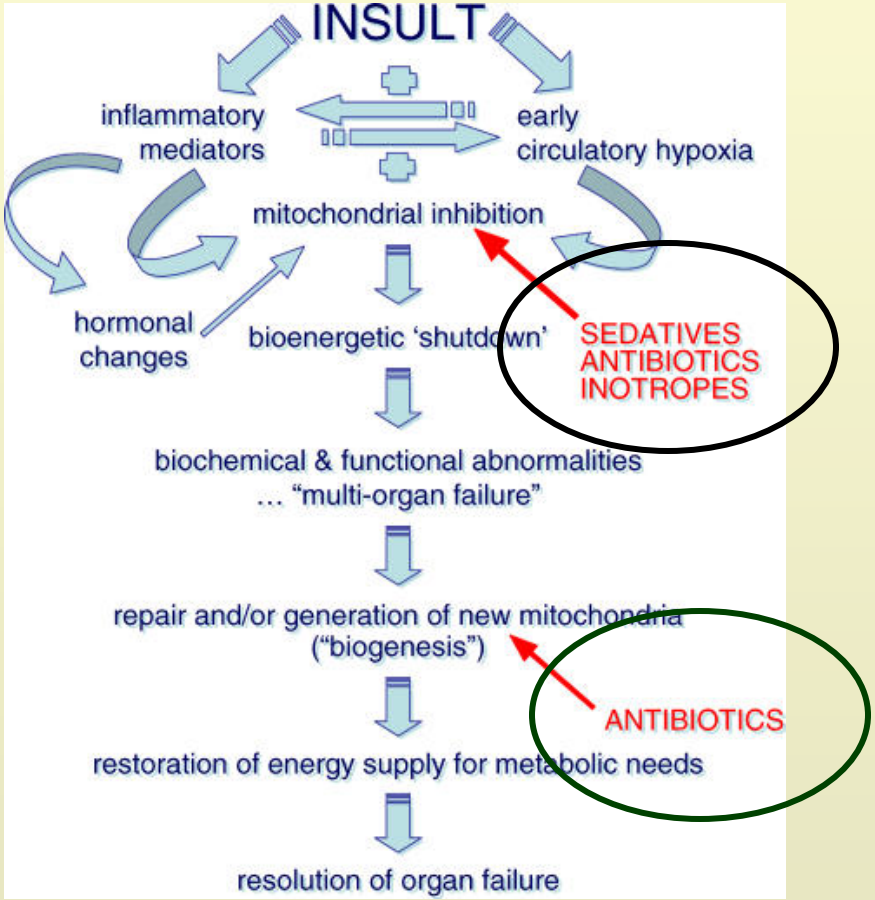
Antibiotics

one sword, two edges

- ☞ May promote mitochondrial damage and shutdown.
- ☞ May interfere with mitochondrial biogenesis and delay recovery.



Singer. Plos Med 2005. e167

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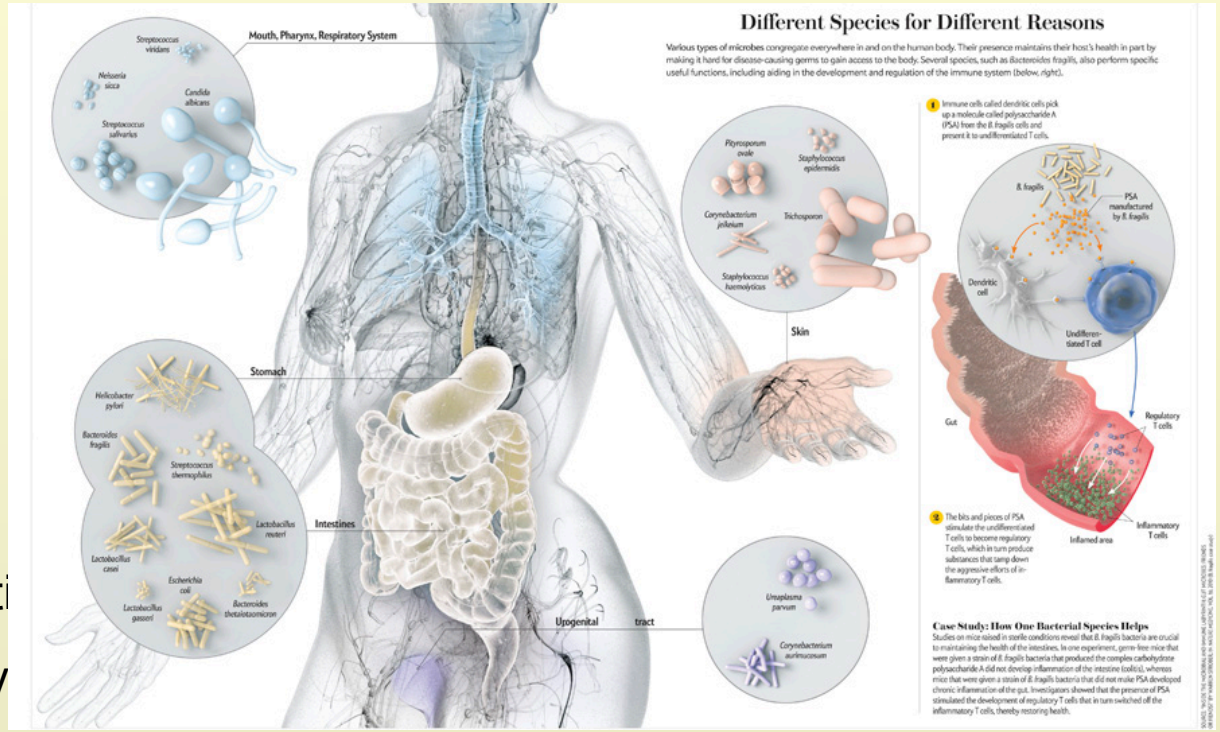
Antibiotics

one sword, two edges

Antibiotics

- Antibiotics help cure infecti

  that the human immune sy



But they also kill all susceptible bacteria, either virulent or not, including the natural flora

the microbiome

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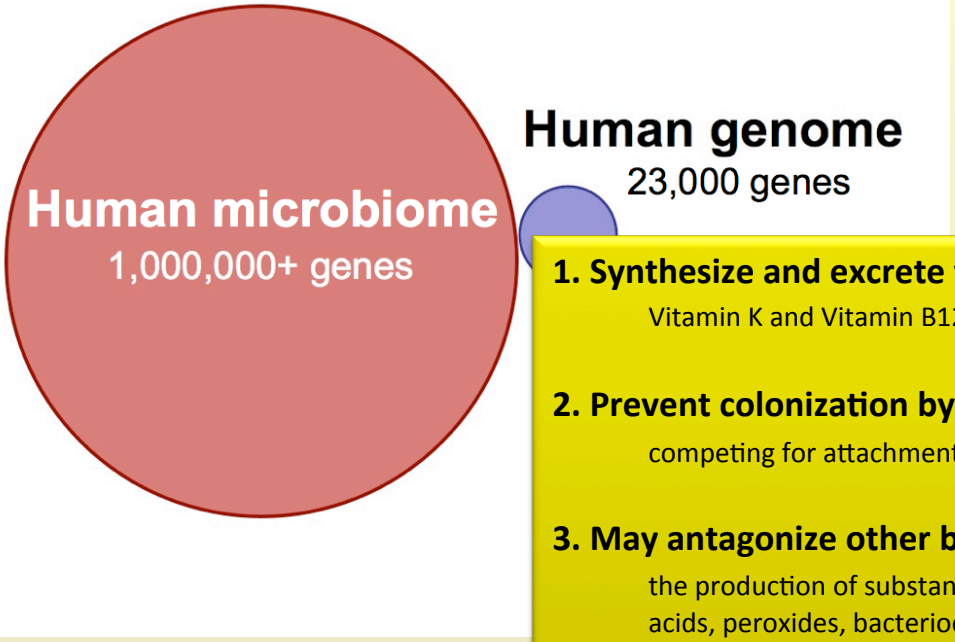
Microbiome



Bacterial cells outnumber body cells 10:1 and comprise up to roughly 3kg of human body mass

1. Synthesize and excrete vitamins

Vitamin K and Vitamin B12

2. Prevent colonization by pathogens

competing for attachment sites or for essential nutrients

3. May antagonize other bacteria

the production of substances which inhibit or kill non-indigenous species(nonspecific fatty acids, peroxides, bacteriocins).

4. Stimulate the development of certain tissues

i.e., intestines, certain lymphatic tissues, capillary density

5. Stimulate the production of cross-reactive antibodies.

Low levels of antibodies produced against components of the normal flora are known to cross react with certain related pathogens, and thereby prevent infection or invasion.

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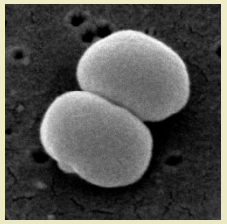
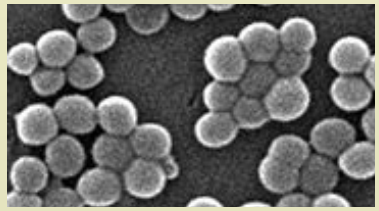
Microbiome

Most human surfaces contains a wide variety of microbes normally found there, well balanced, **e.g., the skin flora:**

- *Staphylococcus epidermidis* bacteria forms a biofilm that coats the mucosal lining



- *Staphylococcus aureus* bacteria is kept under control by a protease found in *S. epidermidis*, but if left to grow out of control, *S. aureus* can become pathogenic and cause infection



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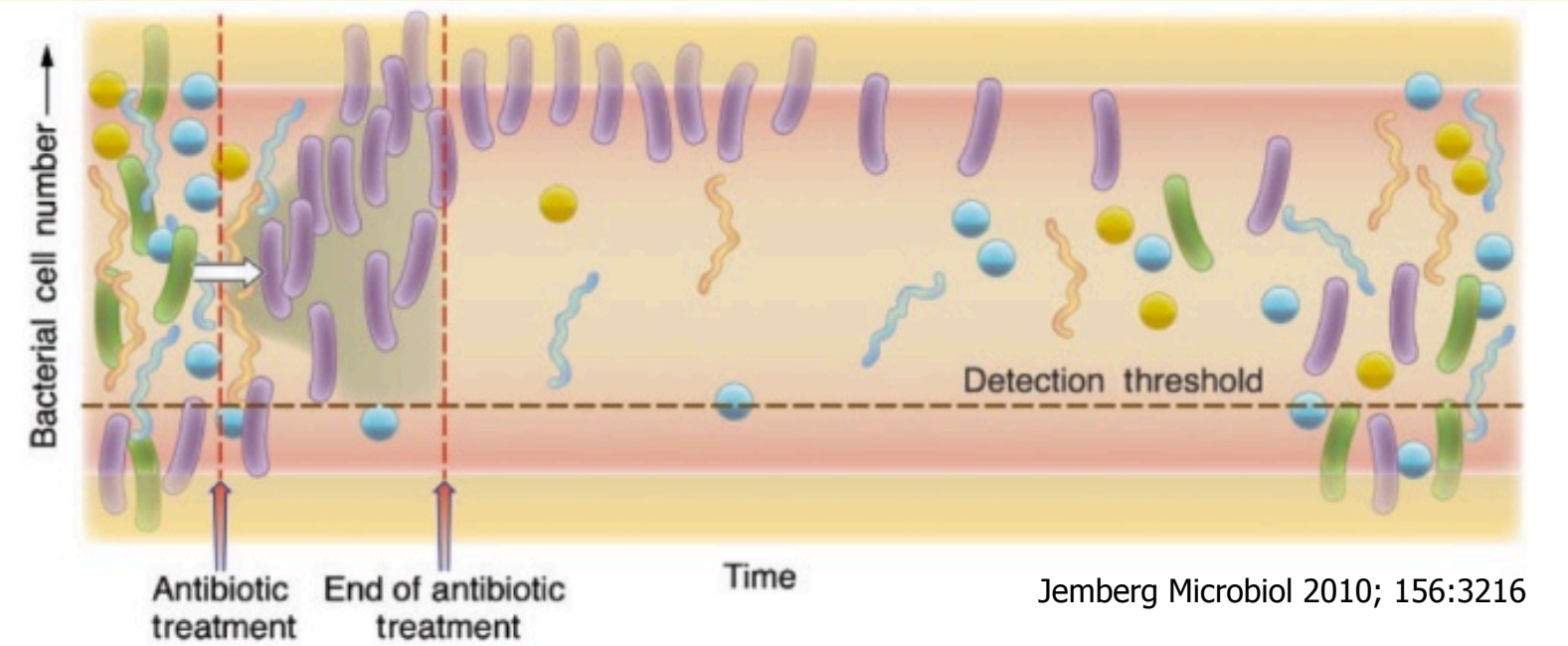
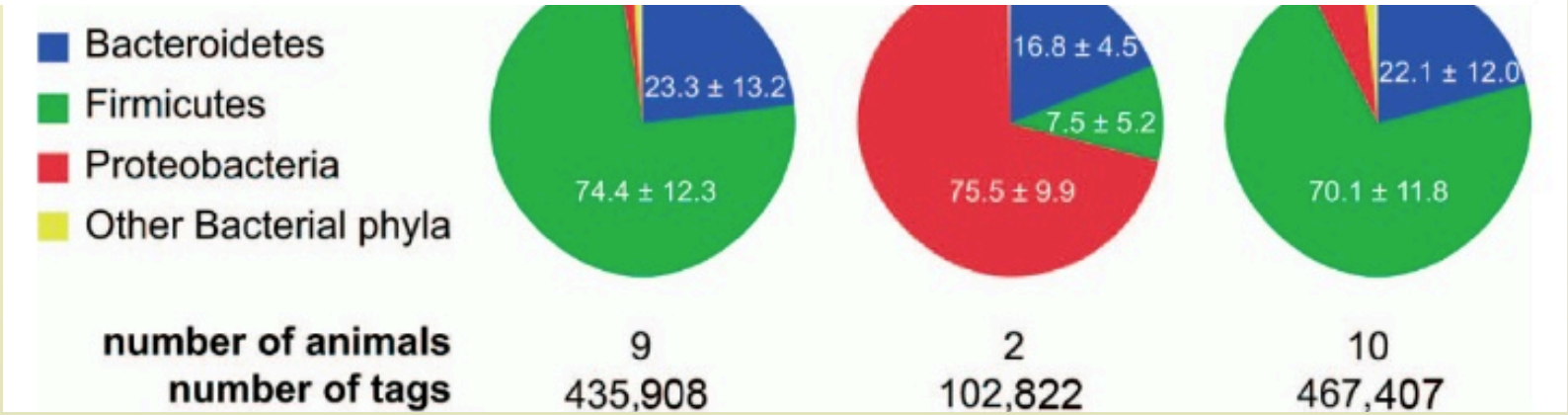
Antibiotics and human microbiome



Jemberg Microbiol 2010; 156:3216



Antonopoulos, Inf Immunit 2009; 77:2367

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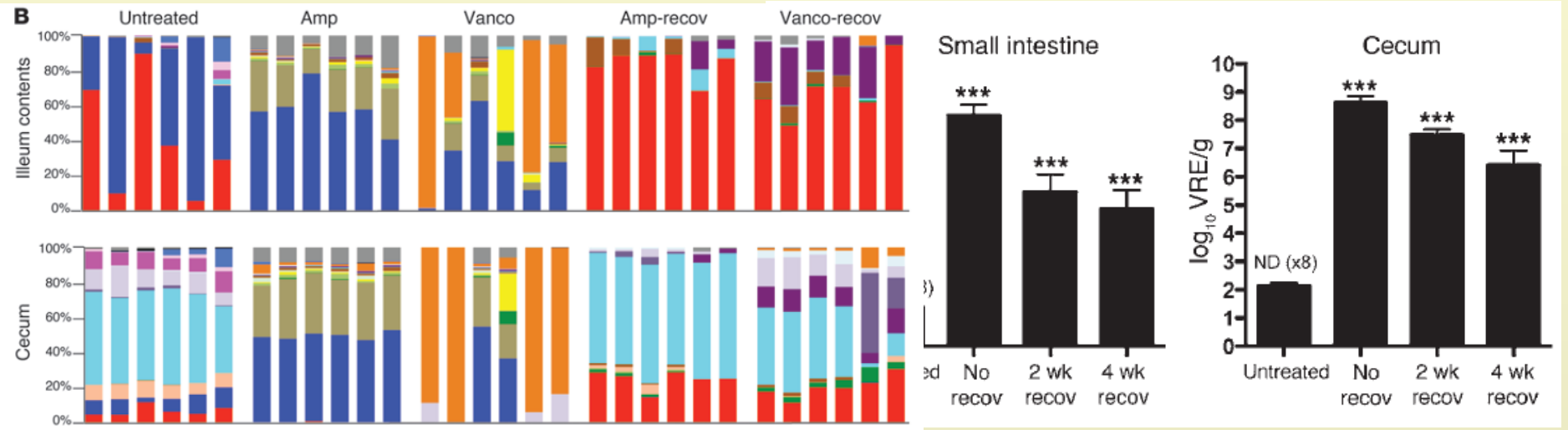
Vancomycin-resistant *Enterococcus* domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans

Carles Ubeda,[1,2] Ying Taur,[1] Robert R. Jenq,[3] Michele J. Equinda,[1,2] Tammy Son,[3] Miriam Samstein,[1,2] Agnes Viale,[4] Nicholas D. Socci,[5] Marcel R.M. van den Brink,[2,3] Mini Kamboj,[1] and Eric G. Pamer[1,2]



In the clinical setting, we found that intestinal domination by VRE preceded bloodstream infection in patients undergoing allogeneic hematopoietic stem cell transplantation. Our results demonstrate that **antibiotics perturb the normal commensal microbiota and set the stage for intestinal domination by bacteria** associated with hospital-acquired infections. Thus, high-throughput DNA sequencing of the intestinal microbiota could identify patients at high risk of developing bacterial sepsis.

J Clin Invest 2010; 12:4332

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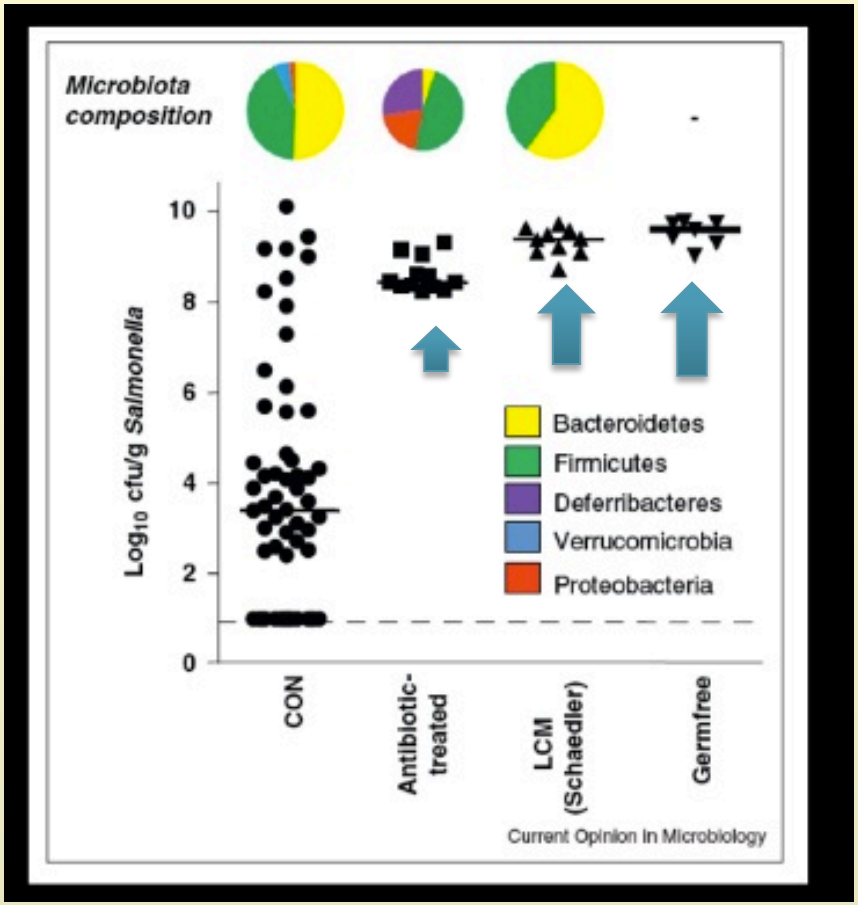
Microbiome and defense against infections

Salmonella invasive infections in mice treated with antibiotics, with low bacteria diversity and germfree

The lower the number and diversity of bacteria, the higher the risk for invasive infections



Stecher Curr Op Microbiol 2010; 14:1

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Bacterial infection

- Most bacteria do not produce disease but achieve a balance with the host that ensures the survival, growth, and propagation of both the bacteria and the host.

- Sometimes bacteria that are clearly pathogens (e.g. *Salmonella typhi*) are present, but infection remains latent or subclinical and the host is a "carrier" of the bacteria.

- Significant Infection indicates multiplication of microorganisms.

- Prior to multiplication, bacteria (in case of bacterial infection) must enter and establish themselves within the host.

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Bacterial infection

Sense environment

- Bacteria can sense changes in environment
  - e.g. in temperature, nutrient availability, osmolarity, cell density ("quorum sensing").
  - In simplest cases, change in intracellular concentration of ion linked directly to gene expression
  - e.g. fall in intra-cellular iron levels triggers de-repression of diphtheria toxin gene

- In more complex cases, sophisticated signal transduction cascades allow bacteria to regulate gene expression in response to environmental cues

Switch virulence factors on and off

- Changes in DNA sequence
  - Gene amplification
  - Genetic rearrangements
    - e.g. Hin flip-flop control of flagellar phase variation
- Transcriptional Regulation
  - Activators and Repressors (helix-turn-helix motif)
  - mRNA folding and stability
- Translational Regulation
- Post-translational Regulation
  - Stability of protein, controlled cleavage
  - Covalent modifications
    - e.g. phosphorylation in two-component sensor-regulator systems

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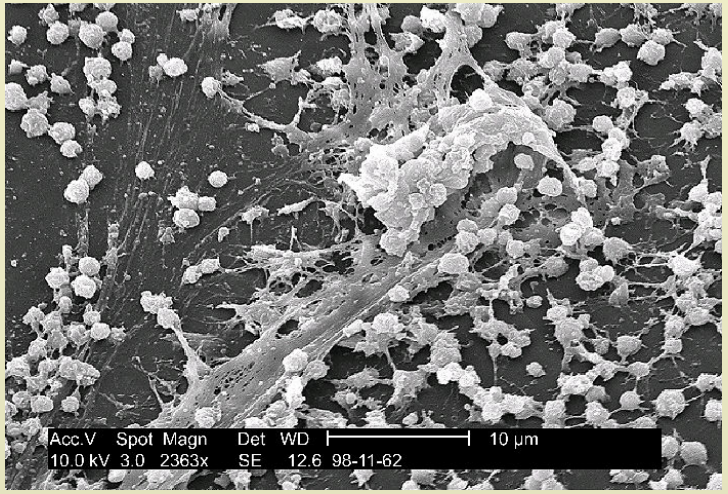
Biofilms

>99% microbes live in a biofilm

- Whereas conventional microbiology has concentrated on planktonic organisms

- Planktonic
  - From Greek ‘wandering’
  - Free floating form

- Sessile
  - From Latin ‘sitting’
  - Fixed to a site (usually an organic/ inorganic surface)



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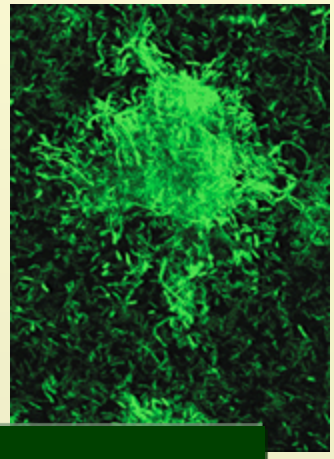
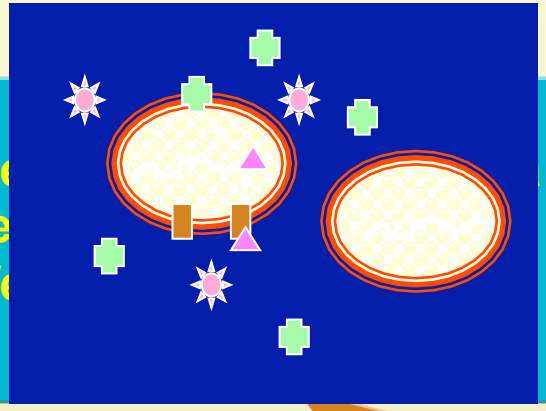
Biofilms

Colonization: *Quorum sensing*

Bacteria cells seems harmless when multiplying





Signaling moleculles

- Self / non Self
- Number

aches a the cal changes

- Metabolism

☞ **Virulence Factors**

☞ **Biofilms**

Structured, cooperative microbial community embedded in an extracellular matrix, usually attached to a surface

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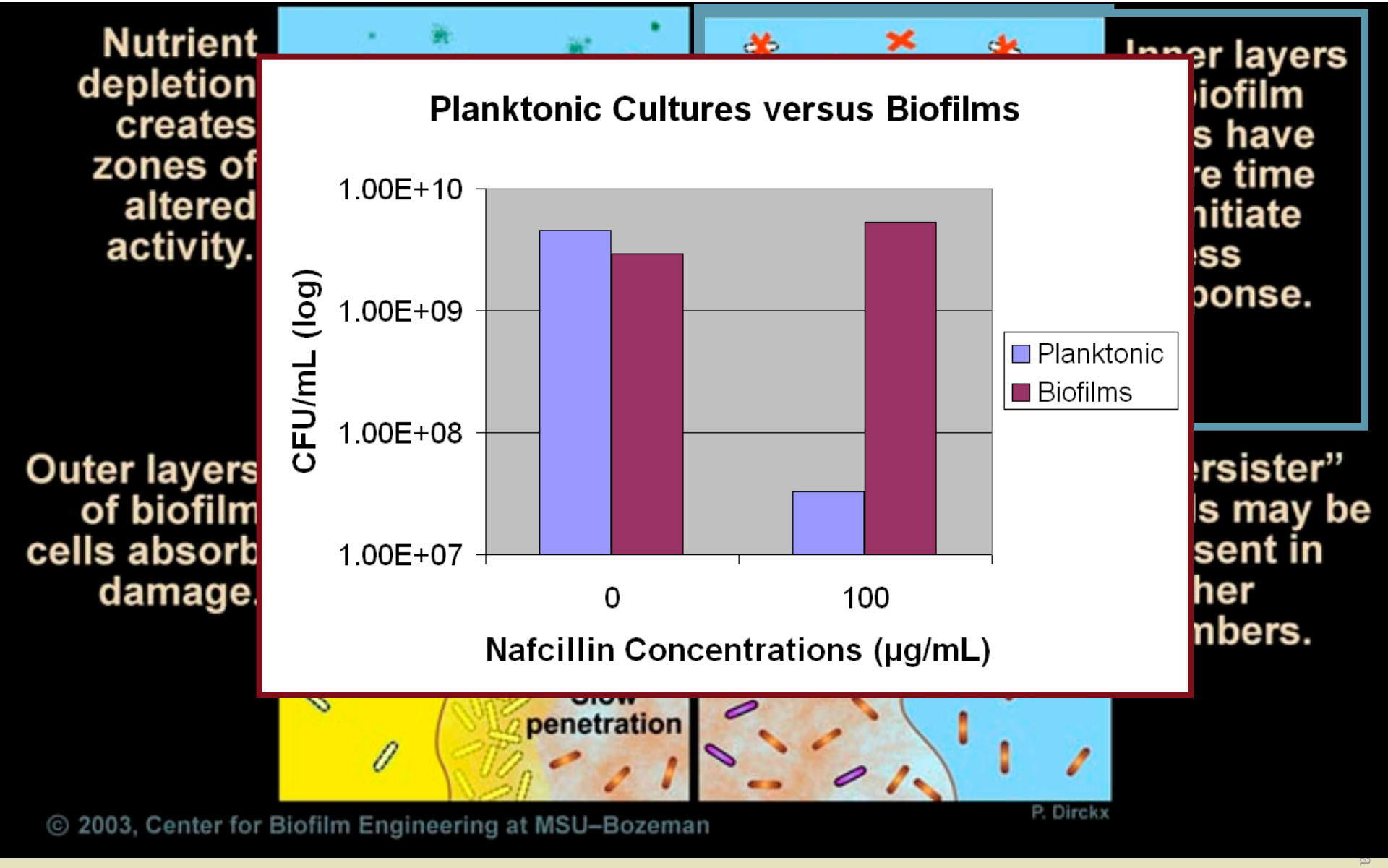
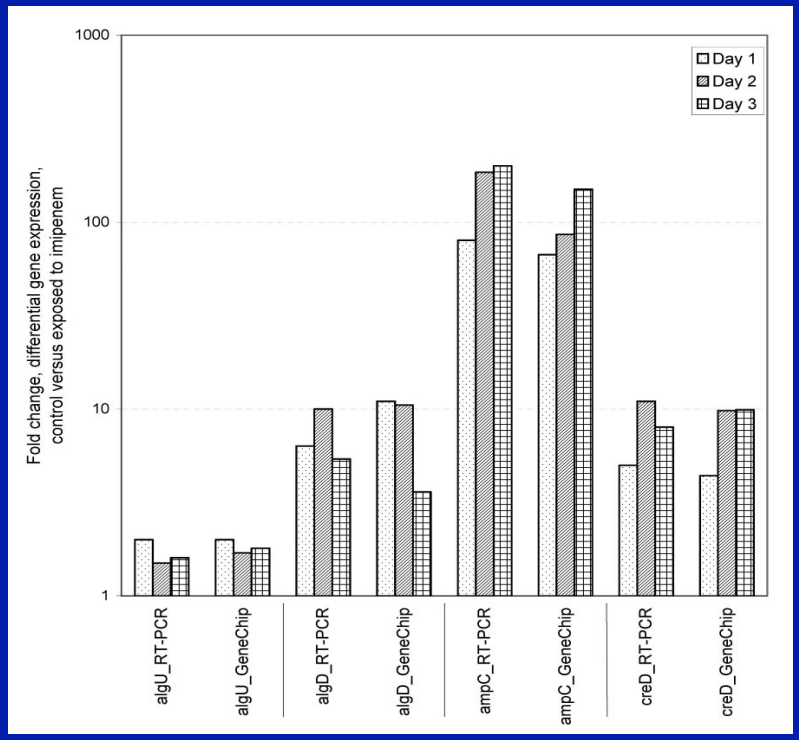
MIC: Biofilms



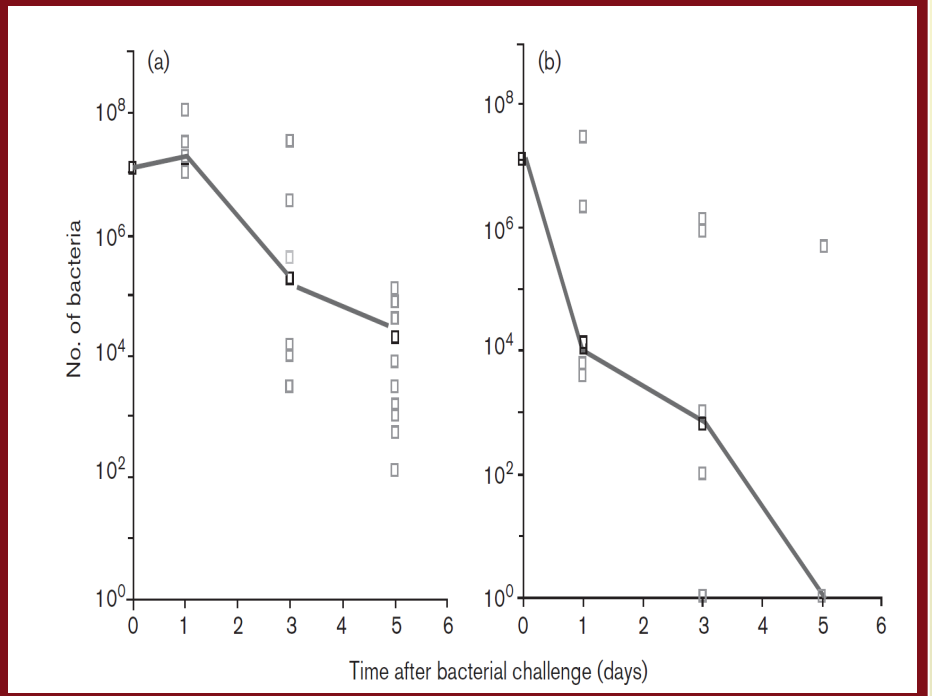
Biofilms

Pseudomonas aeruginosa gene induction in biofilms by subinhibitory concentrations of **imipenem**



Bagge Antimicrob Agents Chemother 2004;48:1175

Garlic inhibits *Pseudomonas aeruginosa* biofilms in a pneumonic mice model



Bjarnsholt Microbiology 2005;151:3873

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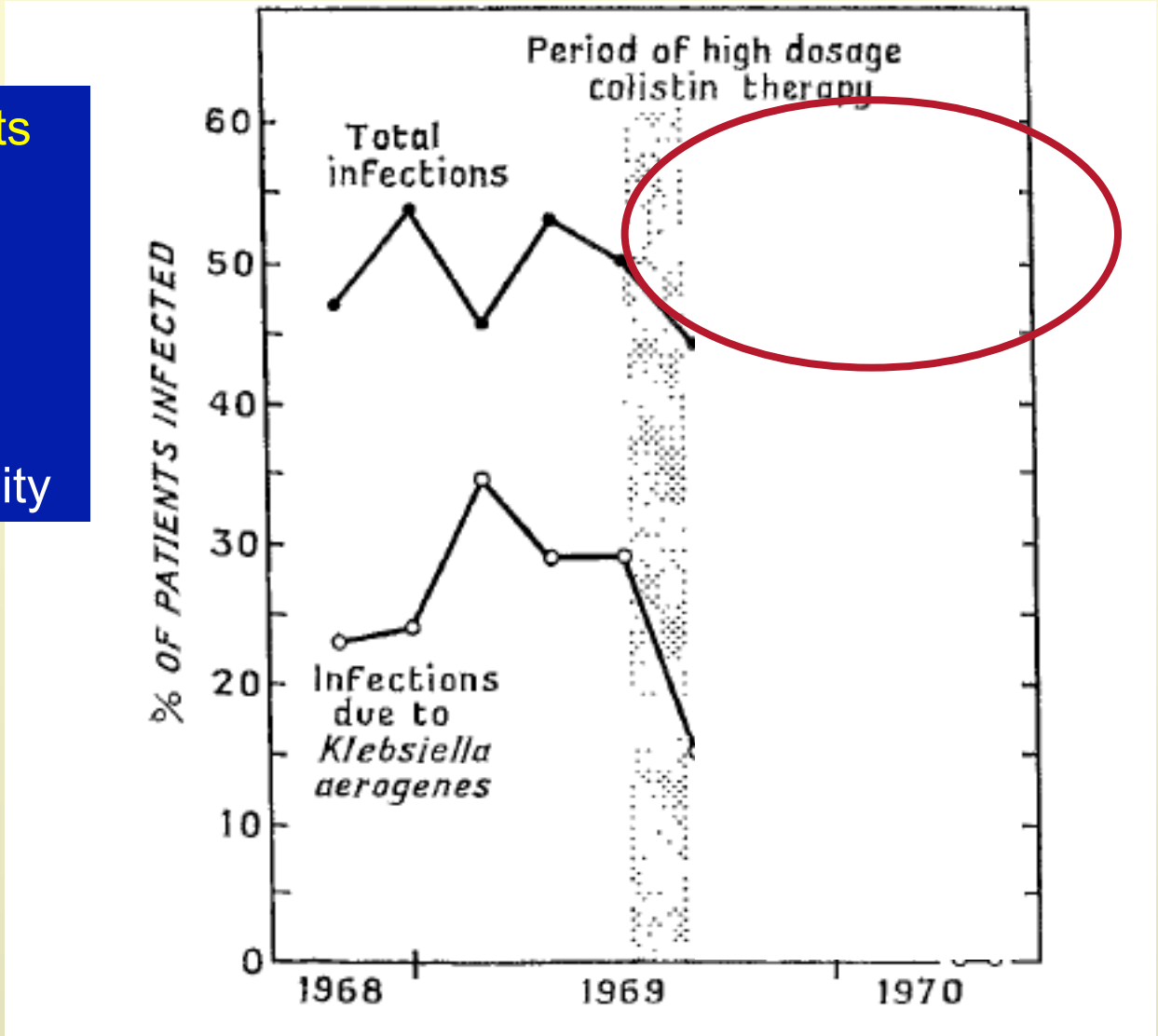
Interventions to Decrease Antibiotic Resistance

Neurosurgical patients

Klebsiella aerogens

High LOS

Increase Mortality



Price, Lancet 1970; 1213

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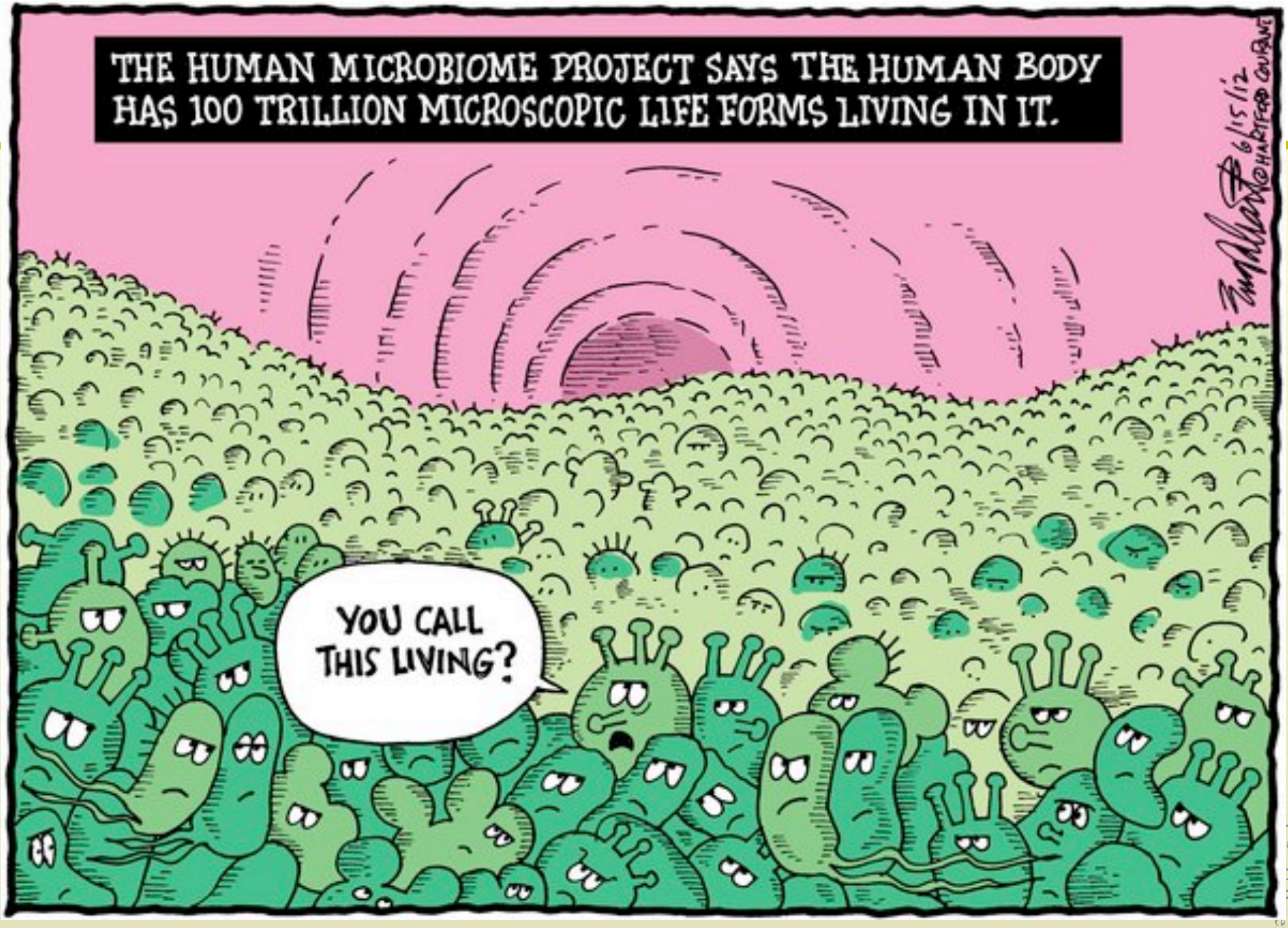
THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.
YOU CALL THIS LIVING?