ECCMID 2013

Breaking Barriers Among Antibacterial Strategies: The Patient, the Group, and the Environment

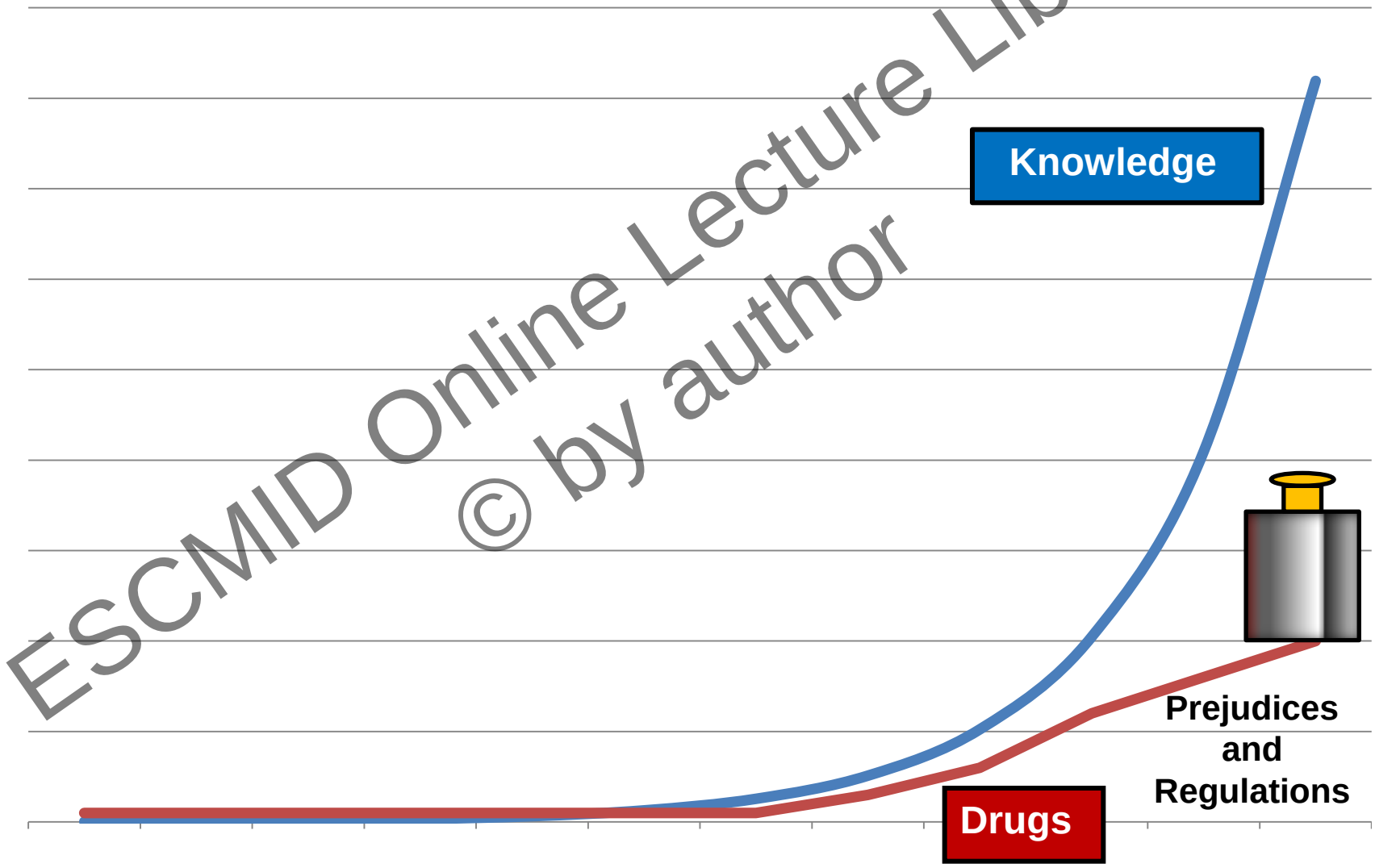
Fernando Baquero

Department of Microbiology

Ramón y Cajal University Hospital

Madrid, Spain

Knowledge, Drugs, Prejudices and Regulations

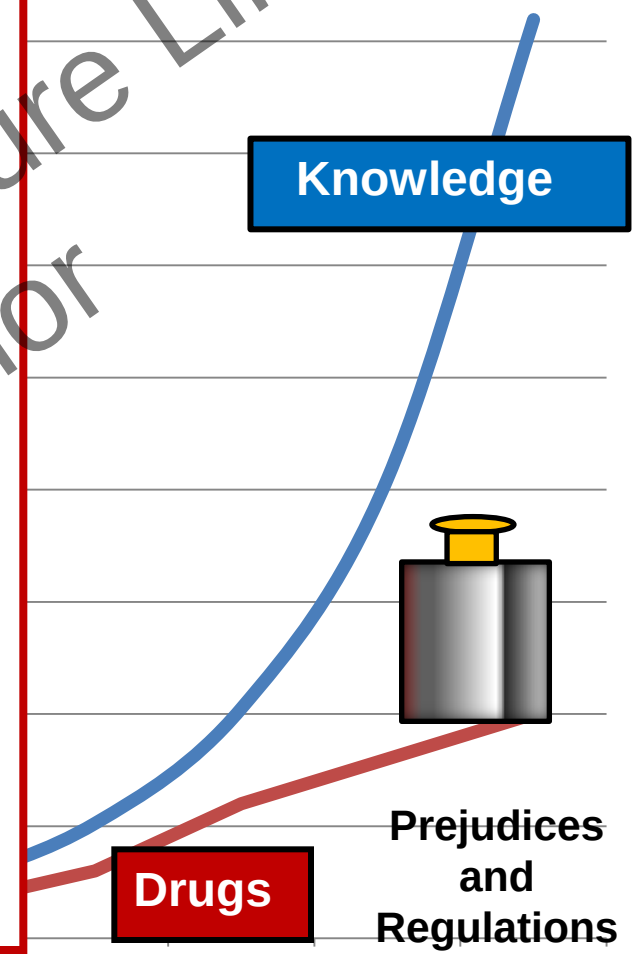


Knowledge, Drugs, Prejudices and Regulations

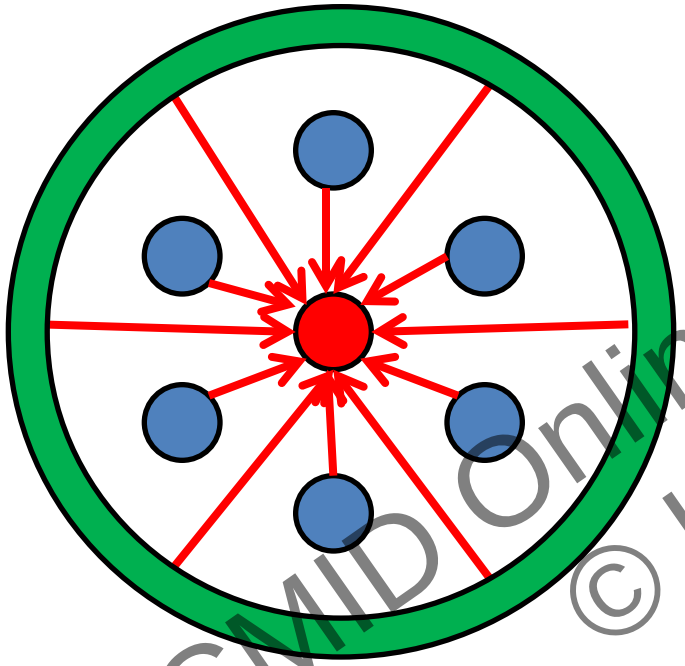
Some Classic Prejudices

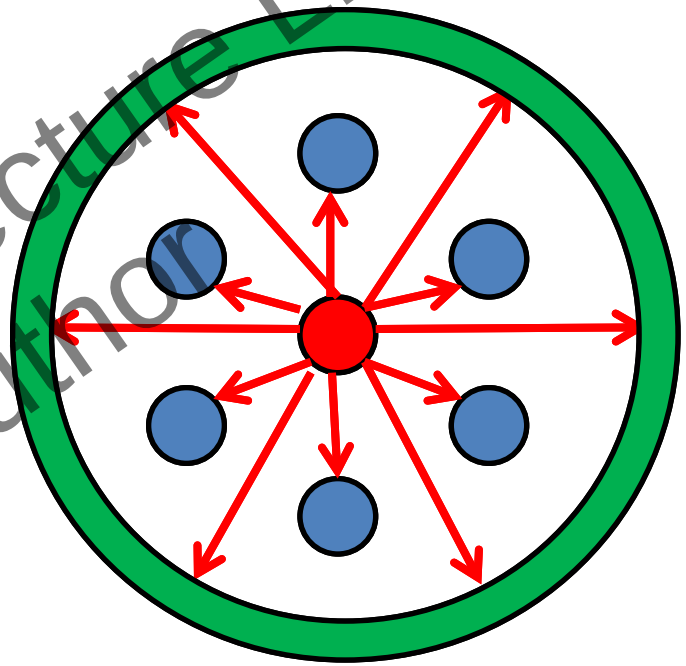
- Single Genes/Proteins as targets
- Full enzyme or cell inhibition required
- Only drugs with low MICs matters
- PK based on conventional MICs
- The need of being cidal, cell killers
- Large spectrum required
- Absence of toxicity required
- Very low “mutation rate”
- Never treat a non-infected patient
- Drug combinations anathemitized
- “One infection, one germ, one antimicrobial”

- The inmutable concept of what is a “drug”
- The inmutable “single-drug” clinical assay



The Individual, Group, and Environment Continuum





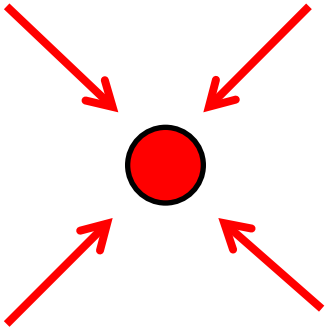
The classic view:

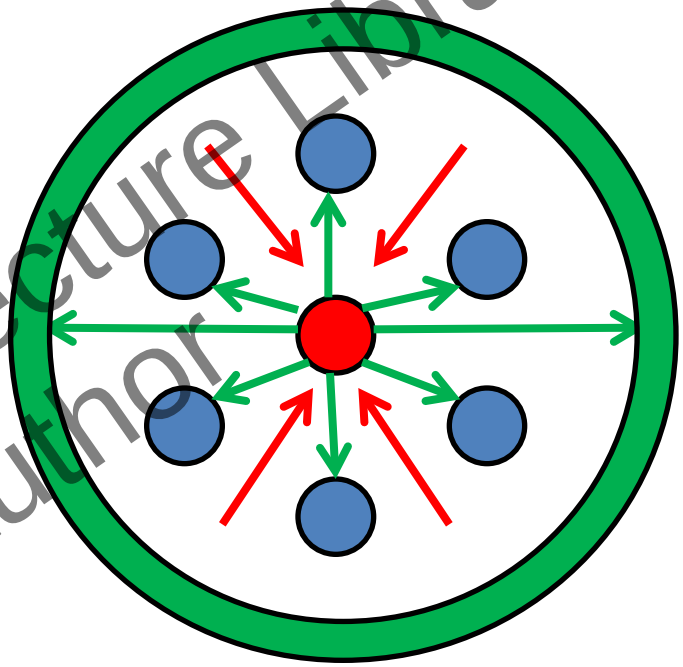
The group and the environment as cause of the individual infection

The other side of the coin:

The infected individual as cause of group and environmental sickness

Personalized Interventions AND Particular Group and Environment Interventions





Personalized Anti-infective Interventions

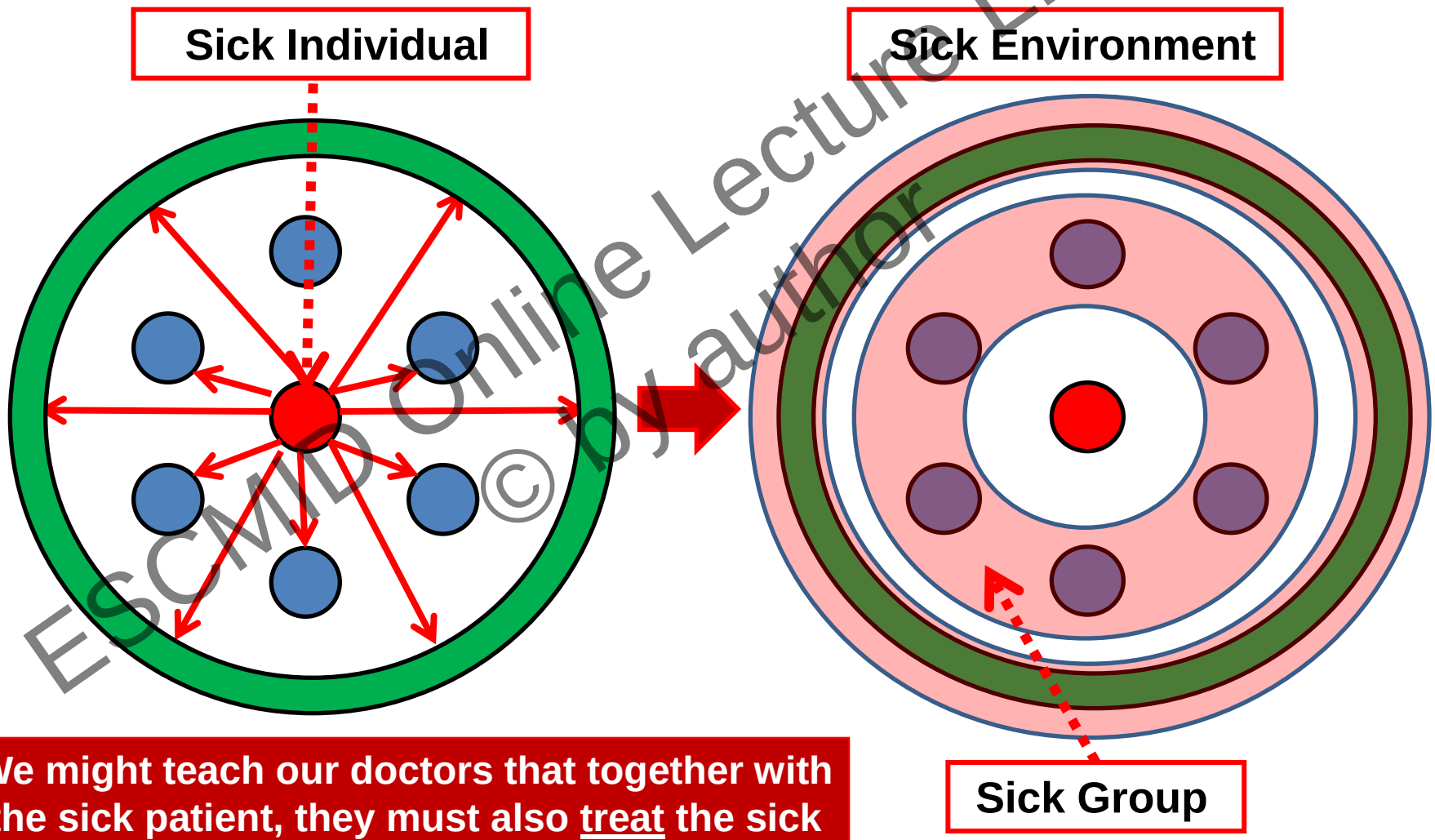
The individual patient as target

Personalized Anti-infective Interventions

AND

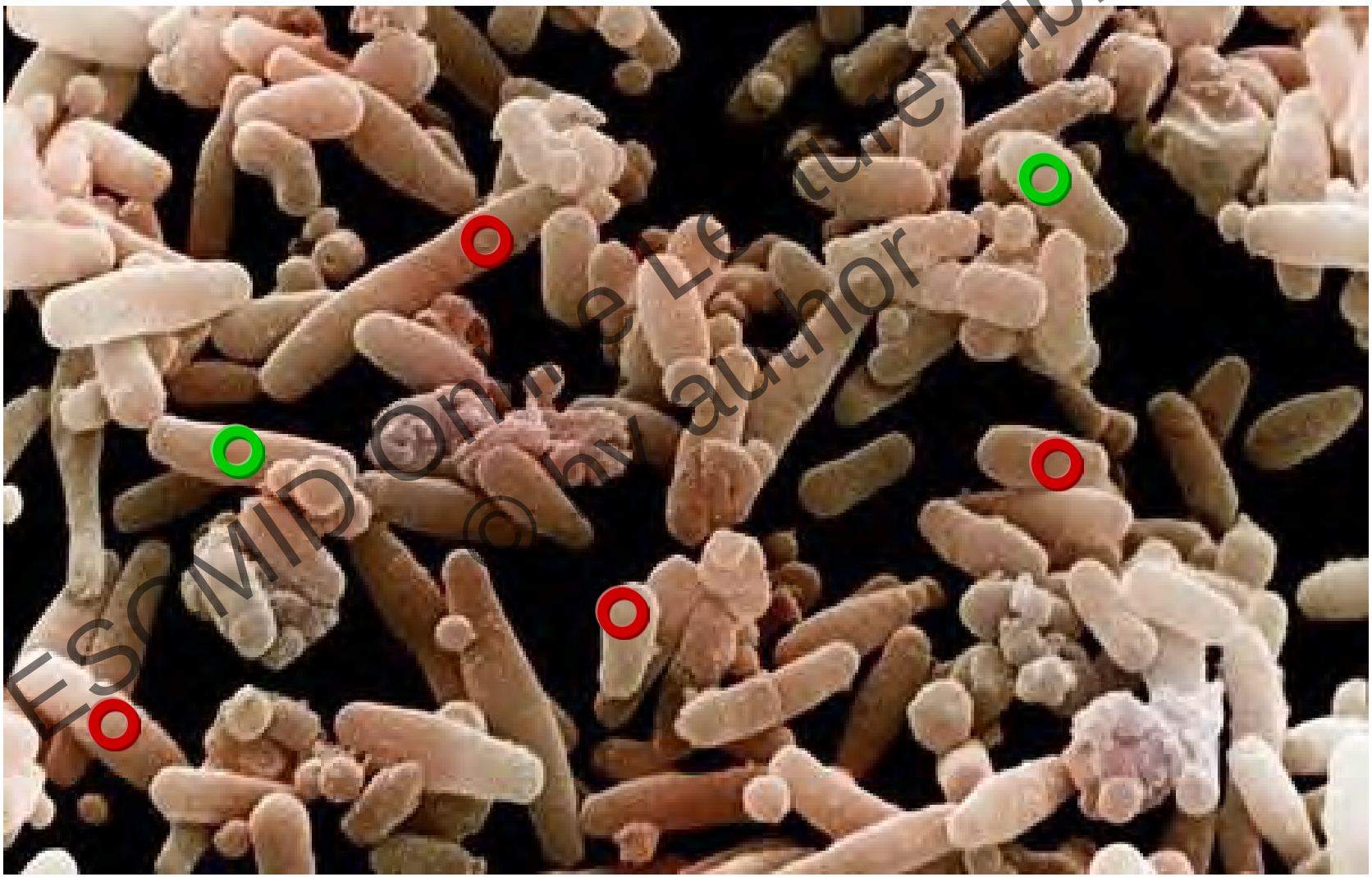
Interventions from the individual patient to the group and the environment

From sick individual to sick environment



We might teach our doctors that together with the sick patient, they must also <u>treat</u> the sick group and the sick environment

Sick Microbiota



Sick Microbiota because of Resistance

Sick Environment

Sick water because of antibiotic resistance

UNEP | UN HABITAT

This report, compiled by GRID-Arendal has been an interagency collaboration led by UNEP and UN-HABITAT in partnership with members of UN Water.

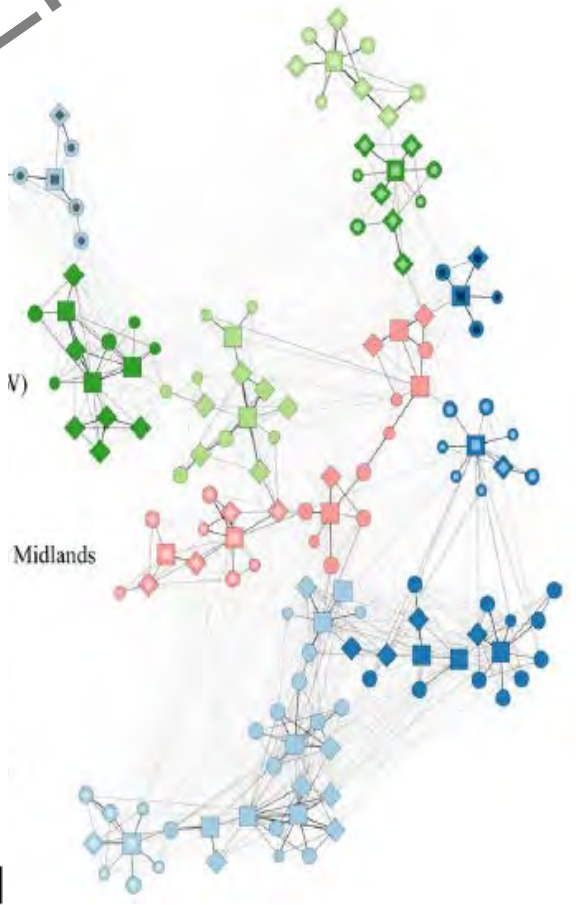
Corcoran, E., C. Nellemann, E. Baker, R. Bos, D. Osborn, H. Savelli (eds). 2010. *Sick Water? The central role of wastewater management in sustainable development.* A Rapid Response Assessment. United Nations Environment Programme, UN-HABITAT, GRID-Arendal. www.grida.no

ISBN: 978-82-7701-075-5

Printed by Birkeland Trykkeri AS, Norway

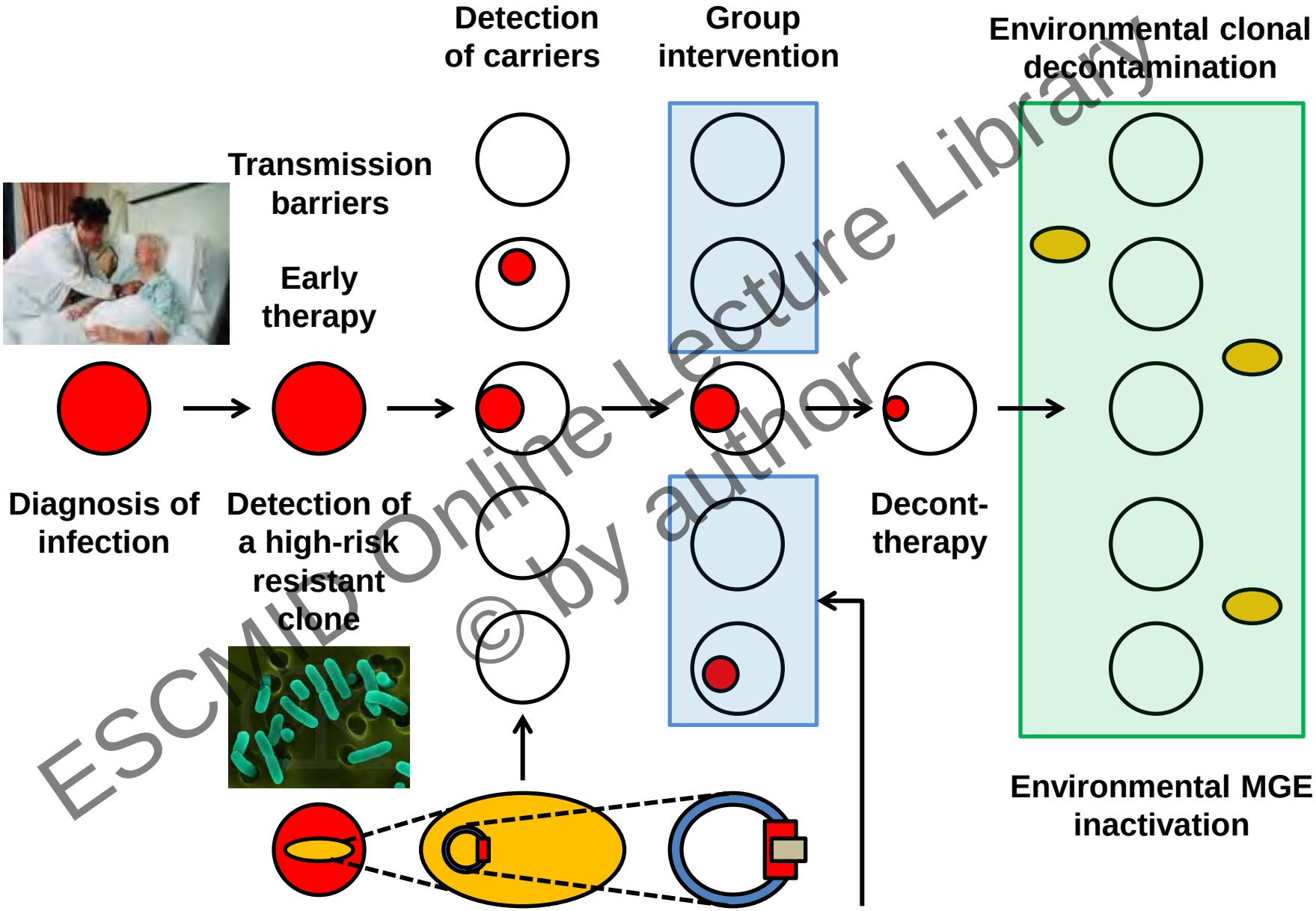
United Nations Environment Programme (UNEP)- UN HABITAT

Sick Hospital



The Structure of a Hospital Referral Network

Grundmann H PLoS One 7(4):e35002 (2012)



Transmission barriers

Early therapy

Detection of carriers

Group intervention

Environmental clonal decontamination

Antibiotic therapy for the group; examples in *S. pyogenes, N. meningitidis, C. trachomatis, M. tuberculosis*….

Diagnosis of infection

Detection of a high-risk resistant clone

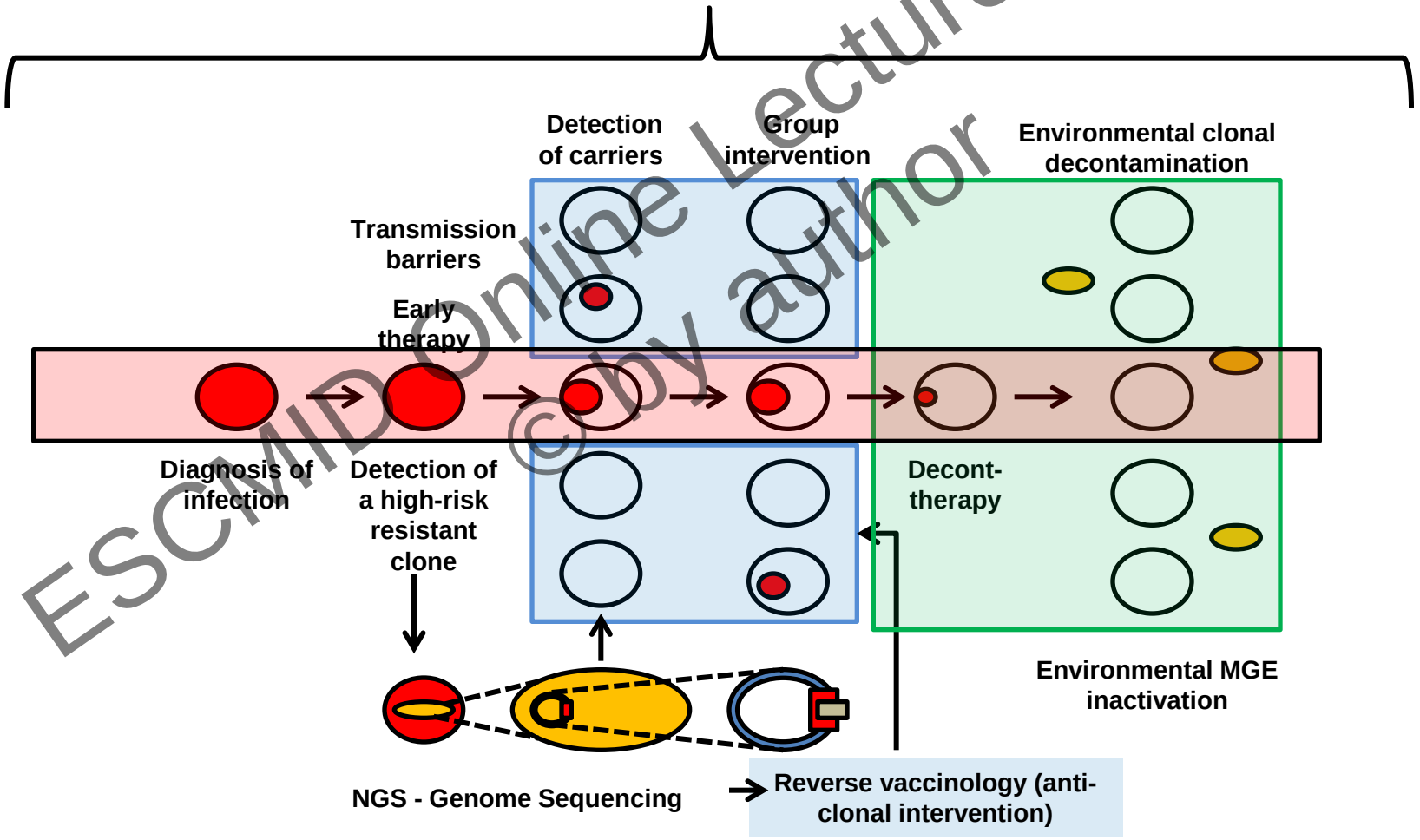
Decont-therapy

Environmental MGE inactivation

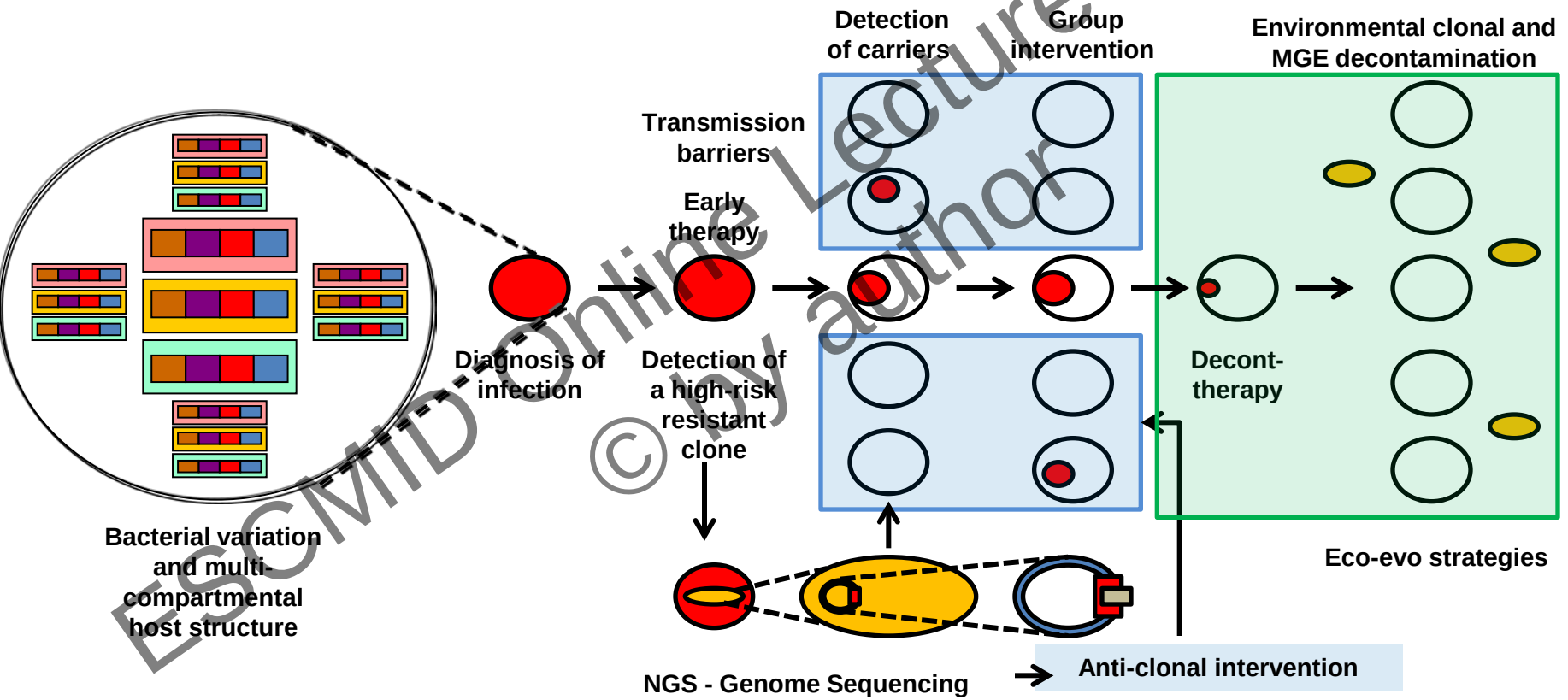
NGS - Genome Sequencing → Anti-clonal intervention –

The individual, the group, and the environment

Multi-compartment antimicrobial interventions

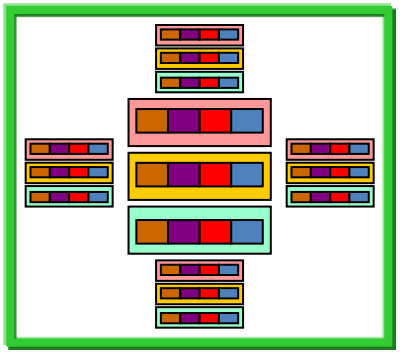


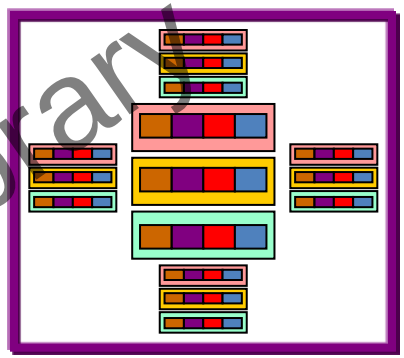
Multiple Compartments and Complex Integrated Therapy



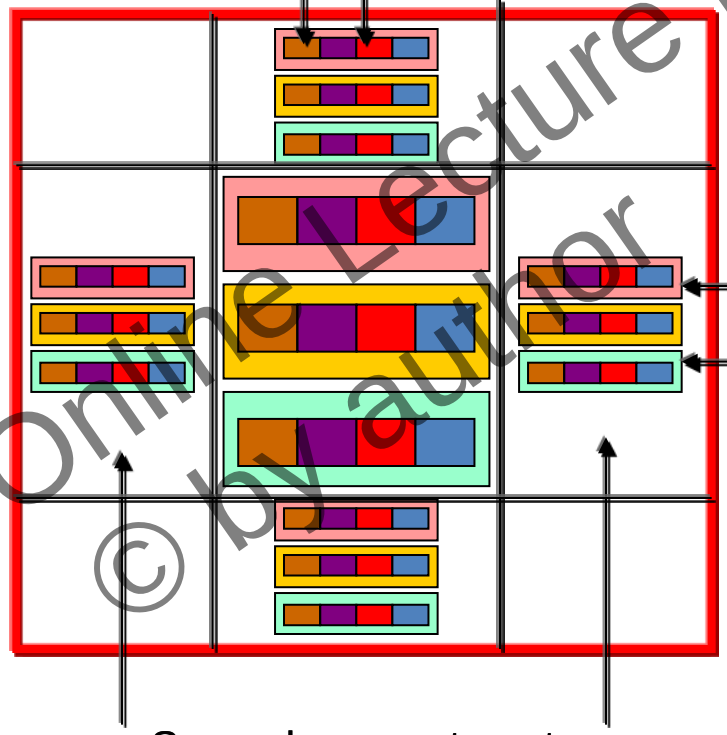
(a single case!!)

Antibacterial Drugs Dealing with a Highly Complex System



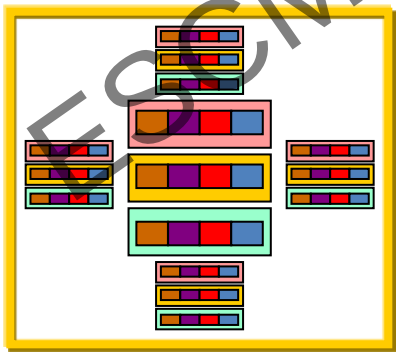


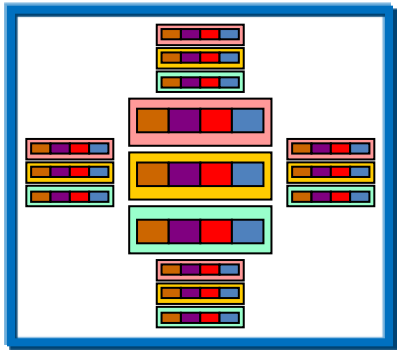
Several targets in a cell



Several phenotypes in a cell/population

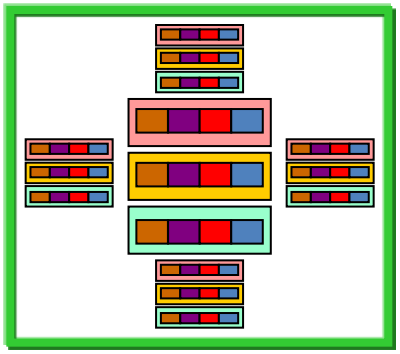
Several compartments within a host

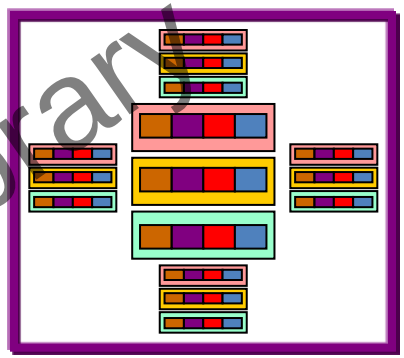




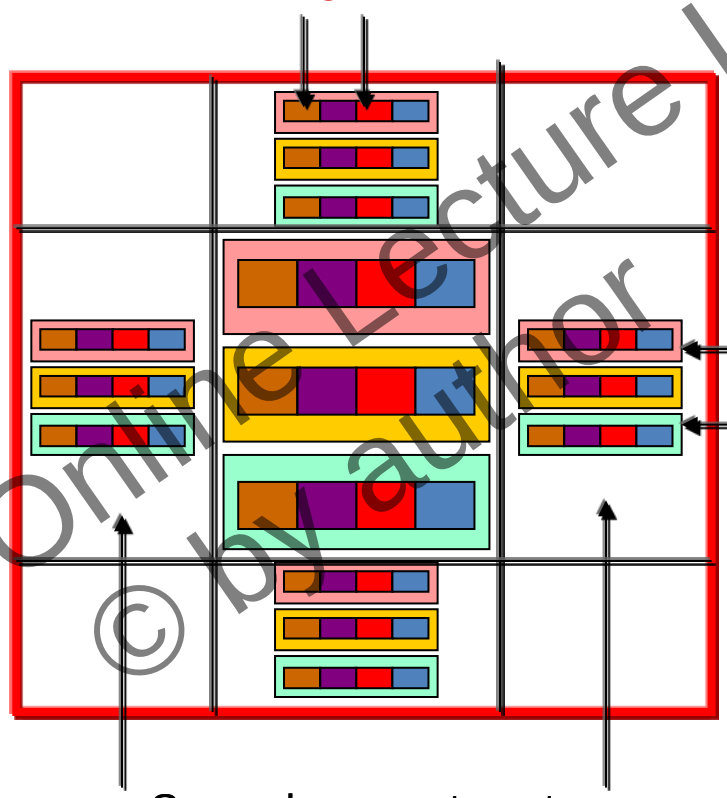
Several types of hosts within a group

Multi-targeted antimicrobial therapy; Combined therapy



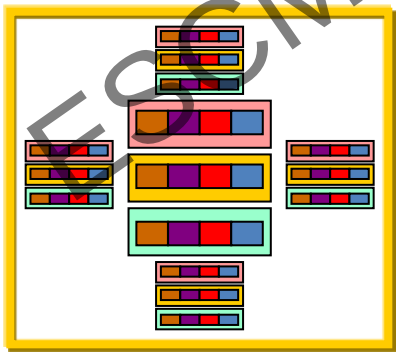


Several targets in a cell



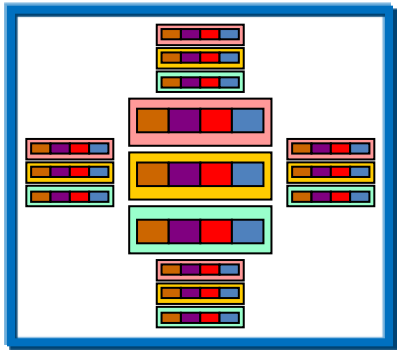
Several phenotypes in a cell/population

Personalized Antimicrobial Therapy

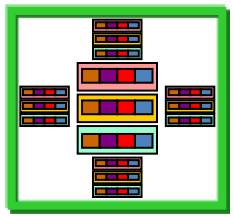


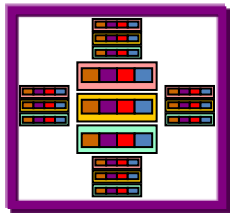
Several compartments within a host

Several types of hosts within a group

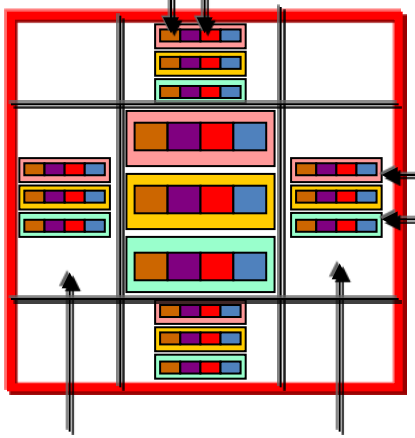


Antibacterial Drugs Dealing with a Highly Complex System

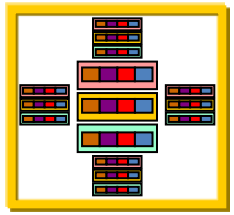




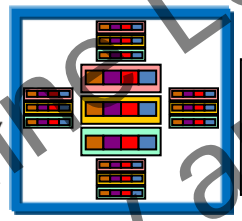
Several targets in a cell



Several phenotypes in a cell/population

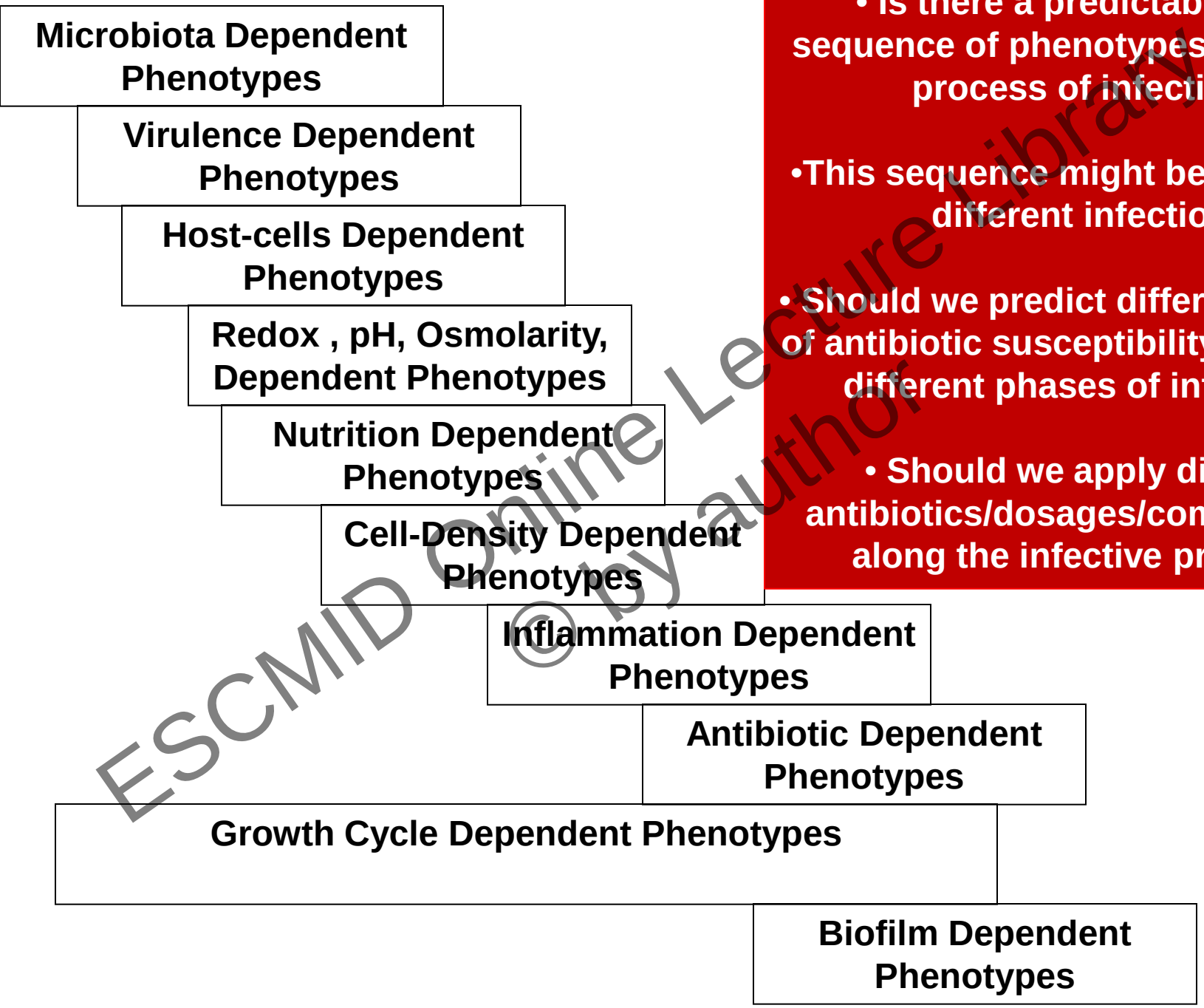


Several compartments within a host
Several types of hosts within a group



Explosive *in-vivo* Phenotypes Diversification

- **Nutrition Dependent Phenotypes**
- **Cell-Density Dependent Phenotypes**
- **Growth Cycle Dependent Phenotypes**
- **Virulence Dependent Phenotypes**
- **Host-cells Dependent Phenotypes**
- **Biofilm Dependent Phenotypes**
- **Microbiota Dependent Phenotypes**
- **Antibiotic Dependent Phenotypes**
- **Redox, ph, osmo, temp. - dependent Phenotypes**
- **Inflammation Dependent Phenotypes**



Transmission barriers

Early therapy

Detection of carriers

Group intervention

Environmental clonal decontamination

Diagnosis of infection

Detection of a high-risk resistant clone

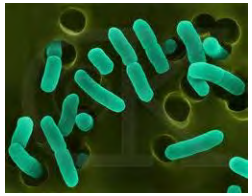
Decont-therapy

Environmental MGE inactivation

NGS - Genome Sequencing

Reverse vaccinology (anti-clonal intervention)

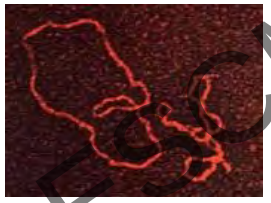
Gene-decontamination



Antibiotics, Anticlonal therapy

Anti-integration and recombination

Vaccination, Disinfection

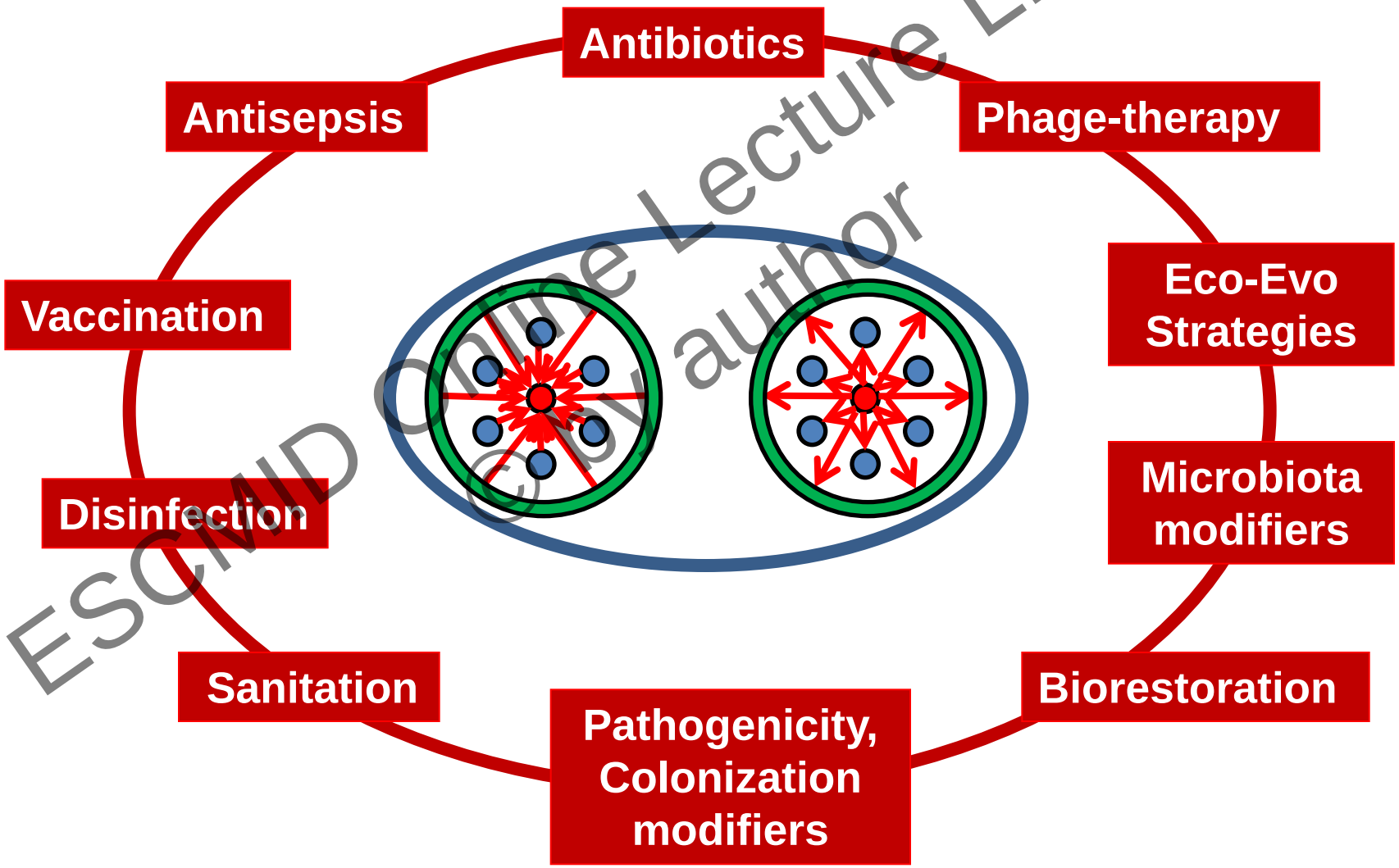


Anti-plasmid , conjugation inhibitors

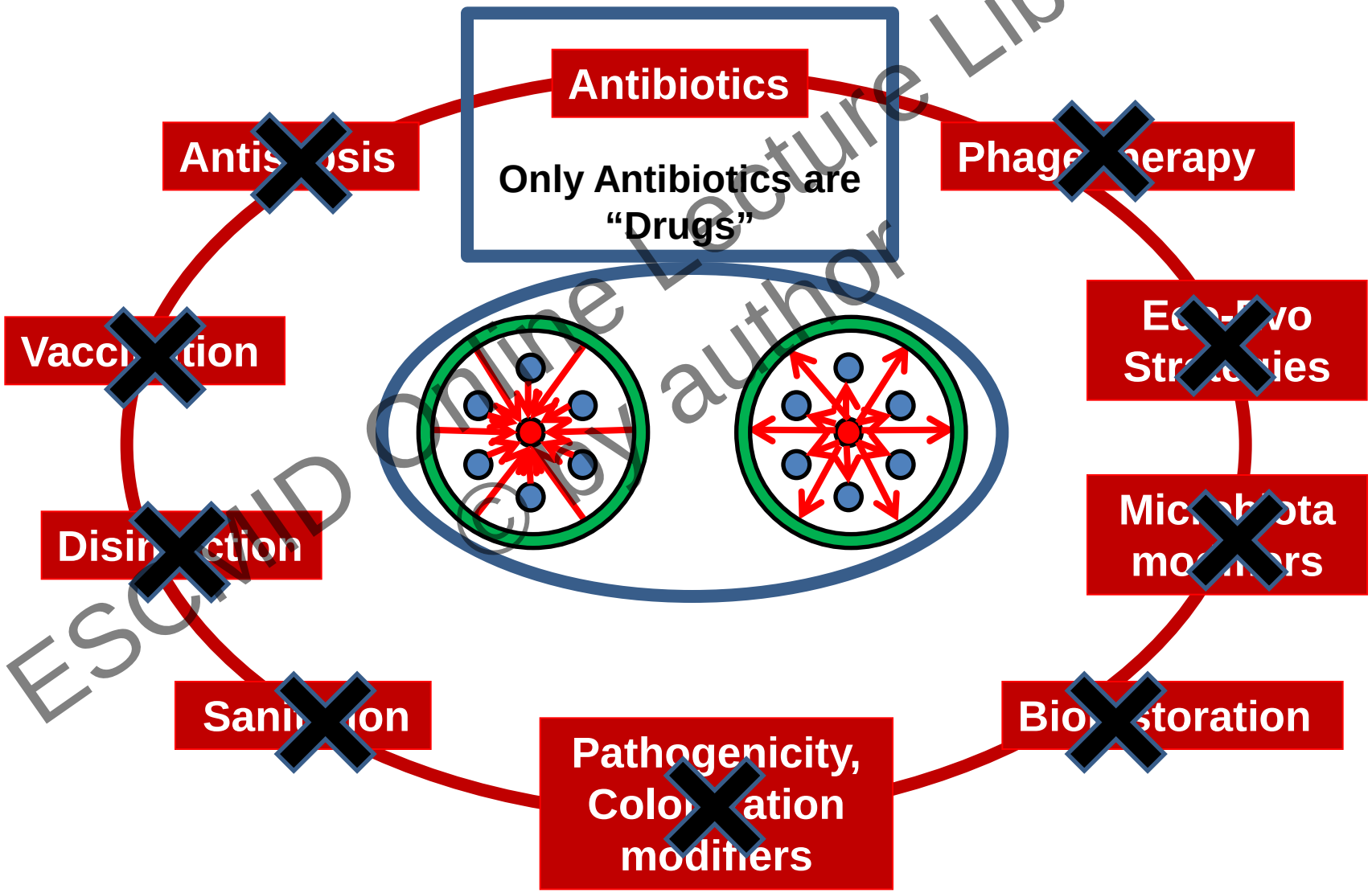
Sanitation, Decontamination

Multi-level Therapy of Infection in an Holistic Perspective

Convergence of anti-bacterial “therapies”



Convergence of anti-bacterial “therapies”



What is an antimicrobial drug?

- An antimicrobial drug is a **chemical-pharmaceutical product** of natural, synthetic, or semisinthetic origin, **impeding the multiplication of infective agents**, **administered to a patient** accordingly to precise schedules for **treatment or prevention** of **infectious diseases**, either unspecifically (broad-spectrum drugs) or specifically (antituberculous, antimalarials..). **Antibiotics are antimicrobial drugs**.

- **Vaccines are not drugs**, but can be **chemical or biological medicines**, administered to a group of **non-infected** individuals at risk of infection, indirectly **reducing the possibility of multiplication of infective agents** in the hosts that they might reach.

What is an antimicrobial drug?

- An antimicrobial drug is a **chemical-pharmaceutical product** of natural, synthetic, or semisinthetic origin, **impeding the multiplication of infective agents**, **administered to a patient** accordingly to precise schedules for **treatment or prevention** of **infectious diseases**, either unspecifically (broad-spectrum drugs) or specifically (antituberculous, antimalarials..). **Antibiotics are antimicrobial drugs**.

- **Vaccines are not drugs**, but can be **chemical or biological medicines**, administered to a group of **non-infected** individuals at risk of infection, indirectly **reducing the possibility of multiplication of infective agents** in the hosts that they might reach.

Vaccines as "drugs for the groups"?

- **Biocides are not drugs**, but can be **chemical or biological "medicines"**, applied to a contaminated environment **reducing the possibility of multiplication of infective agents** in the environment.

Biocides as "drugs for the environment"?

Breaking barriers among anti-infectives

	Bacterial viability as primary target	**Possible Interaction with host functions**	External / Internal use	Individual or Group as primary target	Example
Systemic Antibiotics	Y	Y	I	I	Beta-lactams
Topical Antibiotics	Y	Y/N	E	I	Mupirocin
Systemic Antiseptics	Y	Y	I	I	Nitrofurantoin
Topical Antiseptics	Y	Y/N	E	I	Hexachlorophene
Disinfectants	Y	N/Y	E	I/G	Povidone Iodine
Anti-resistance mechanisms	N	N/Y	I/E	I/G	Beta-lactamase inhibitors
Anti-virulence in bacteria	N	N/Y	I/E	G/I	Anti-quorum HSL inhibitors
Anti-colonization in bacteria	N	N/Y	E	G/I	Biofilm inhibitors
Anti-host receptors	N	Y	I/E	I	Type III secretor systems inhibitors
Bacteriophages	Y/N	N/Y	I/E	G/I	
Interference (probiotics, amensalism)	N/Y	N/Y	E	I	*E. coli* Nissle 1917
Decolonization	N/Y	N/Y	E	G/I	Intestinal decolonization, fecal transplants
Immunomodulation	N	Y	I	I	
Anti-toxins	N	N/Y	I/E	I/G	Anti-tetanus
Antibiotic deactivators	N	N/Y	E	I/G	Antibiotic-binding compounds
Anti-M-GM-HGT (Eco-Evo)	N	N/Y	E	G/I	
Immunotherapy	N/Y	Y	I	I	Anti-pneumococcal immune sera
Vaccines	N/Y	N/Y	I	G/I	Anti-Haemophilus B vaccination

Systems Biology and Multi-Compartmentalized Anti-Bacterial Strategies

- The National Institute of Allergy and Infectious Diseases recently initiated the **Systems Biology Program for Infectious Disease Research**.
- Bacterial pandemics remain, food and waterborne illnesses are frequent, multidrug-resistant microbes are on the rise, and the **needed drugs and vaccines have not been developed.**
- Intense research **focus on individual genes and proteins** typical of molecular **biology—have not been sufficient** to address these challenges.

Aderem A. et al., mBio 2(1):e00325-10, 2011

A stronger **systems biology perspective** must now focus on the interactions between **drug, host, infectious bacteria and environment** to foster the long-term success of antibiotic strategies

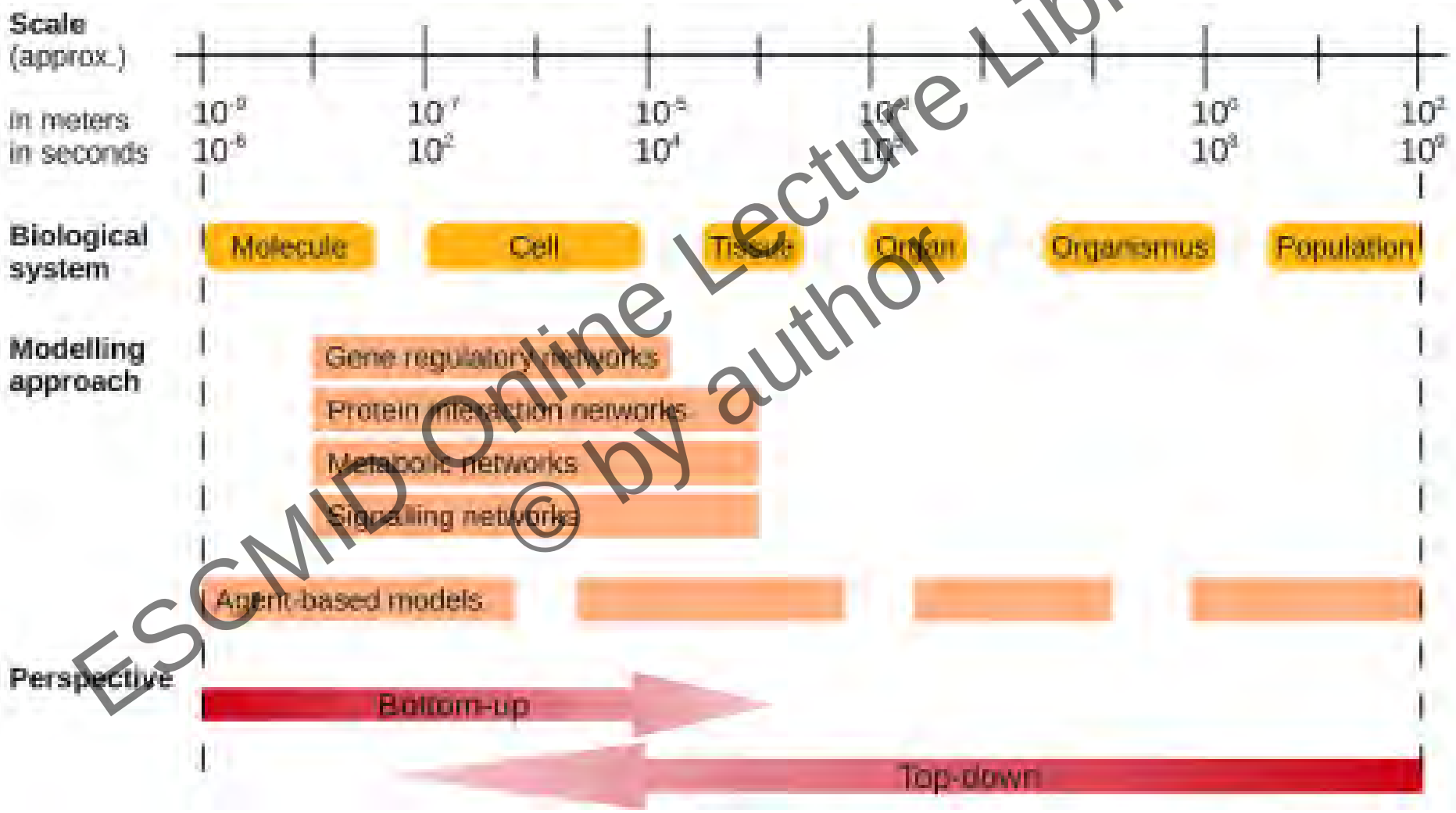
Dandekar T&M. Pharmacogenomics, 11, 2010

Multilevel Analysis of Infectious Diseases

Ana V. Diez Roux and Allison E. Aiello
Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor

The J. of Infect. Dis., 191:S25, 2005

Biological and Modeling levels of System Biology of Infectious Diseases



Horn F et al. Systems biology of fungal infections. Frontiers Microbiol 2012

Eco-Evo Drugs and Strategies

Decontamination of high-risk clones

- **Targeting clones** (**anticlonal vaccines**, **anticlonal phages**)
- **Targeting colonization/virulence** (**antisense** oligomers, peptide-conjugated-**p**hosphorodiamidate **m**orpholino **o**ligonucleotides).
- **Selective decontamination** (classic SDD, novel drugs)
- **Clonal interference** (**probiotics**, genetically modified organisms)
- **Susceptible Microbiota Transplantation**
- **Enhancers of biological cost of resistance**

Intestinal microbiota containing *Barnesiella* cures *E. faecium* colonization (Ubeda C.,Inf.Immun 2013)

Decontamination of mobile genetic elements

- **Plasmid decontamination** (phenotiazines, dibenzoazepines, dibenzocycloheptene, plumbagin, non-absorbable intercalating agents)
- **Plasmid interference, incompatibility**
- **Plasmid maintenance (toxin-antitoxin)**
- (homologs of the hok plasmid factor. GMOs carrying TA homologs)

Decontamination of high-risk genes

Antisense oligomers, as phosphorothioate oligonucleotides (PS-ODNs), locked nucleic acids (LDAs), 2*e*OMes, phosphorodiamidate morpholino oligonucleotides (PMOs), peptidic nucleic acids; short double-stranded RNAs –small interfering RNAs)

Edgar R, et al. (2012) Reversing bacterial resistance to antibiotics by phage-mediated delivery of dominant sensitive genes. AEM A78: 744-751.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2011, p. 3649–3660 Vol. 55, No. 8
0066-4804/11/$12.00 doi:10.1128/AAC.00132-11

MINIREVIEW

Ecology and Evolution as Targets: the Need for Novel Eco-Evo Drugs and Strategies To Fight Antibiotic Resistance▽†

Fernando Baquero,[1]* Teresa M. Coque,[1] and Fernando de la Cruz[2]

Department of Microbiology, Instituto Ramón and Cajal for Health Research (IRYCIS), CIBER Research Network in Epidemiology and Public Health (CIBERESP), Ramón y Cajal University Hospital, Madrid,[1] and Faculty of Medicine, Cantabria University, Santander,[2] Spain

Sick Environment

Sick water because of antibiotic resistance

UNEP | UN HABITAT

This report, compiled by GRID-Arendal has been an interagency collaboration led by UNEP and UN-HABITAT in partnership with members of UN Water.

Corcoran, E., C. Nellemann, E. Baker, R. Bos, D. Osborn, H. Savelli (eds). 2010. *Sick Water? The central role of wastewater management in sustainable development.* A Rapid Response Assessment. United Nations Environment Programme, UN-HABITAT, GRID-Arendal. www.grida.no

ISBN: 978-82-7701-075-5

Printed by Birkeland Trykkeri AS, Norway

United Nations Environment Programme (UNEP)- UN HABITAT

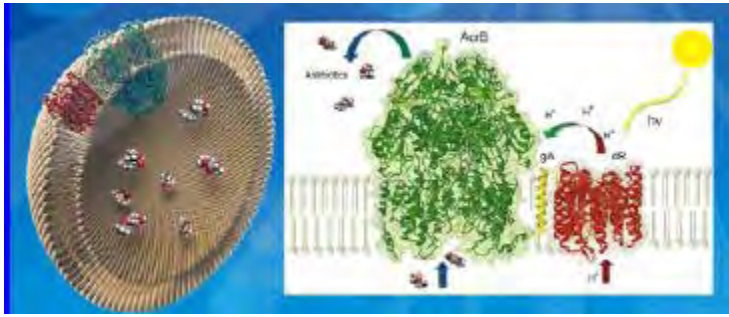
Environmental Restoration of Antibiotic Susceptibility?

- An impossible task?
- Salt, oxygen, chlorine, UV susceptibility of antibiotic-resistant bacteria?
- Biocides more or less active on resistant bacteria?
- How antibiotic-resistant organisms behave in septic tanks?
- Phages against environmental resistance?

Antibiotic elimination from the environment

Kapoor & Wendell. Engineering Bacterial Efflux Pumps for Solar-Powered Bioremediation of Surface Waters.. NanoLetters 2013

Vera, DMA, Tegos GP et al. Anticrobial photoinactivation overcoming resistant phenotypes Photochem Photobiol. 2012



Antibiotics shaping multilevel population biology of bacteria

- Antibiotics increase the **number and evolvability** of "clinical" and "natural" antibiotic resistance genes.
- Antibiotics influence the **abundance, modularity, and spread** of **integrons, transposons and plasmids**.
- Antibiotics **enrich particular bacterial lineages** and clones and contribute to local **clonalization** processes.
- Antibiotics amplify **particular bacterial genetic exchange communities** sharing antibiotic resistance genes and platforms within microbiomes.
- Antibiotic alters the host's **microbiome composition**, facilitating the **interactions between evolutionary units** involved in resistance.

Baquero F, Tedim AP, Coque TM. Frontiers in Microbiology, 2013

Suggested Conclusions

- The infective process influences the individual patient, the group, and the environment
- All these compartments might be simultaneously considered as targets of therapeutical interventions
- Within the individual patient, a complex and variable bacterial organism/s acts within complex sites and variable microecological landscapes.

Complex-integrative antimicrobial therapy probably needed in:

- **Severe cases of infection**
- **Chronic bacterial infections**
- **High-risk and high-transmissible dangerous clones**
- **Emergent dangerous microorganisms**

To Rafael Cantón and Teresa Coque, for long discussions in the lab about the need of complex therapies for complex problems, with strong inputs from Juan-Carlos Galán and Rosa del Campo

Under the Shadow of Systems Biology

- Bio-restoration
- Bio-remediation
- Bio-repair
- Bio-reconstruction
- Bio-decontamination
- Bio-wiring/Bio-rewiring
- Bio-engineering/Bio-reingineering
- Bio-programming
- Bio-modulation/Bio-stimulation
- Bio-augmentation (living catalizer in polluted environment)
- Eco-engineering/Population engineering
- Eco-Therapy
- Trojan Horse Strategies

Could we Cure a Sick Antibiotic-Resistant Environment?

- Biological systems requires the integration of high-throughput multiomics data (transcriptomics, proteomics, metabolomics, lipidomics, etc.), which are used to construct predictive models of the networks and dynamic **interactions between the biological components of the complex pathogen-host system**

  Bumann, D. 2009. System-level analysis of Salmonella metabolism during infection. Curr. Opin. Microbiol. 12:559 –567.

The Resurrection of Combinations

- Tamma PD et al, (2012).Combination therapy for treatment of infections with gram-negative bacteria. Clin Microbiol Rev. 25:450
- Chait R. et al, (2007). Antibiotic interactions that selects against resistance. Nature 446:668
- Pritchard J.R et al., (2012). Defining principles of combination drug mechanisms of action. PNAS.

- Vera DMA, Tegos GP et al. (2012). Strategies to Potentiate **Antimicrobial Photoinactivation** by Overcoming Resistant Phenotypes. Photochemistry and Photobiology, 2012, 88: 499–511

- Lu TK, Collins JJ (2009) **Engineered bacteriophage targeting gene networks as adjuvants for antibiotic therapy**. Proceedings of the National Academy of Sciences of the United States of America 106: 4629-4634