

PHAGEN

EIN VIELVERSPRECHENDER THERAPIEANSATZ

PD Dr. med. Dr. phil. Yok-Ai QUE



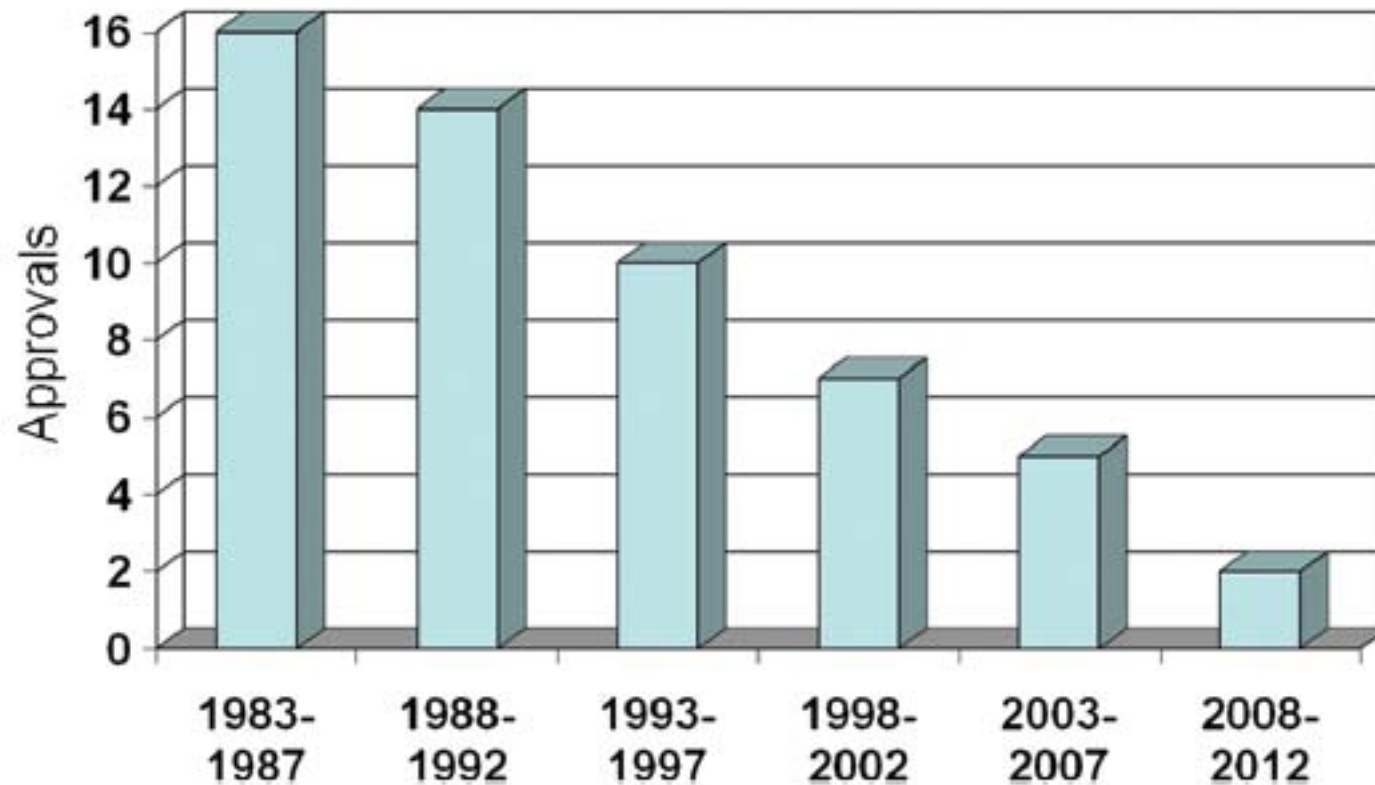
ANTIBIOTIKA RESISTENZ

AUCH EIN PROBLEM IN DER SCHWEIZ !

ANTIBIOGRAMMES	6[C] Pseudomona 01.05.13 SEC TRACHE	7[D] Pseudomona 29.04.13 ABCES (PRE	8 Pseudomona 25.04.13 URINE SOND	9[E] Pseudomona 25.04.13 CENT JUG G	20[B] Pseudomona 02.04.13 MINI LBA	34 Pseudomona 04.02.13 EXP PAR AS
Ampicillin						
Amoxicillin						
Amoxicillin-clavulanate						
Pipéracillin-tazobactam	R	R	R	R	R	sensible
Ceftriaxone						
Ceftazidime	R	R	R	R	R	sensible
Cefepime	R	R	R	R	R	sensible
Imipenem	R	R	R	R	R	R
Meropenem	R	R	R	R	R	I
tapenem						
Aztreonam	R	R	R	R	R	I
Amikacin	R	R	R	R	sensible	sensible
Gentamicin	R	R	R	R	R	sensible
Tobramycin	R	R	R	R	sensible	sensible
Colistin	R	sensible	sensible	sensible	sensible	sensible
Co-trimoxazole	R	R	R	R	R	R
Ciprofloxacin	R	R	I	R	sensible	sensible
Levofloxacin	R	R	R	R	R	sensible
Vancomycin						
Teicoplanin						

BAD BUGS – NO DRUGS

NEUZULASSUNG ANTIBIOTIKA



Boucher HW, CID, 2013, 56:1685–94

BAD BUGS – NO DRUGS

WELCHE STRATEGIE ?

VERFÜGBARE MEDIKAMENTE OPTIMIEREN

WIRKSAMKEIT DER HEUTIGE *ANTIBIOTIKA ERHALTEN*

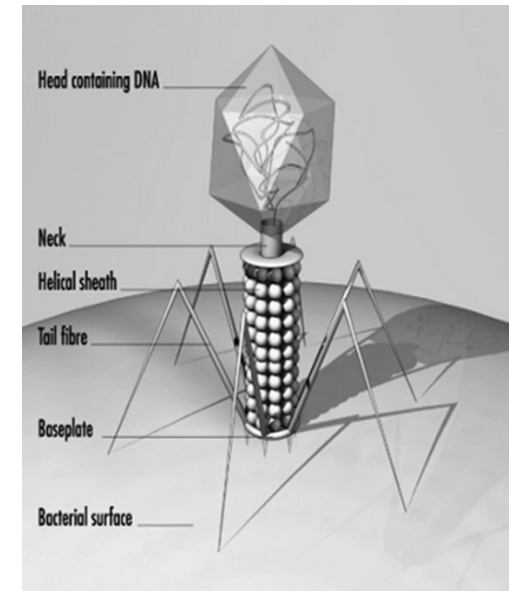
- Prolongierte Infusion für β -lactam Antibiotika verwenden
- Steuerung der Antibiotikatherapie nach Serum Spiegel
- Inhalative Antibiotika

INNOVATIVE STRATEGIE

- **BACTERIOPHAGEN / LYSIN**
- Therapeutische Antikörper
- Antivirulence Strategie
- Antibakterielle Peptide
- Potentiators
- Neue Biomaterialien

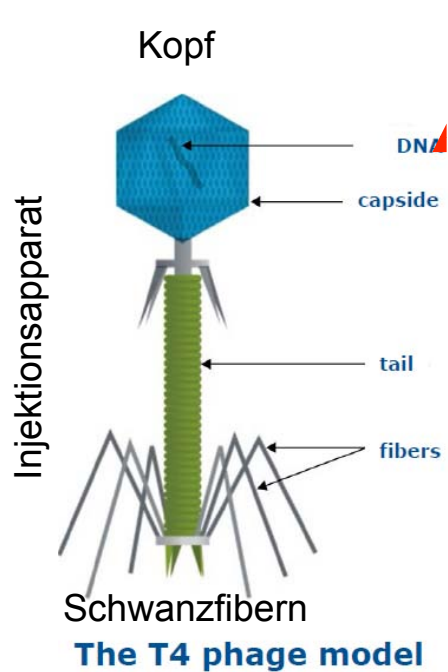
BACTERIOPHAGEN

VIREN GEGEN BAKTERIEN



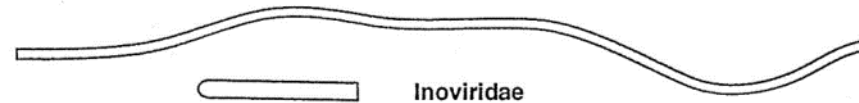
- Die häufigsten lebenden Einheiten der Erde:
4-6 x 10³¹ zehnmal häufiger als Bakterien
 - Überall in der Umwelt: Seen, Flüssen, Pfützen, Gartenerde, Pflanzen, Lebensmittel, Tieren + Menschen (e.g. Darm)
 - Bis 10⁹ Phagen per ml Wasser
 - Bis jetzt keine durch Phagen verursachte Krankheit beschrieben
- Keine Phagen Sequenzen im Menschengenom nachweisbar

BACTERIOPHAGEN KLASSIFIKATION

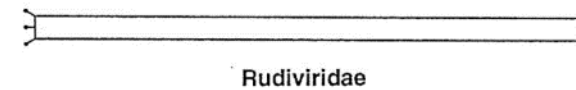
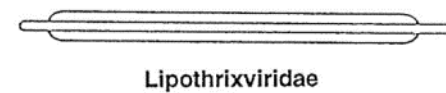
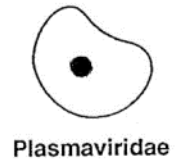
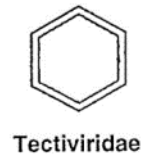
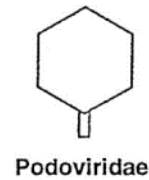
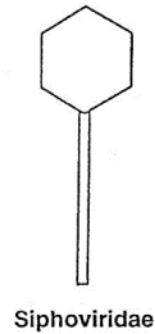
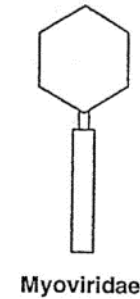


96% *Caudovirales*

ssDNA



dsDNA



ssRNA

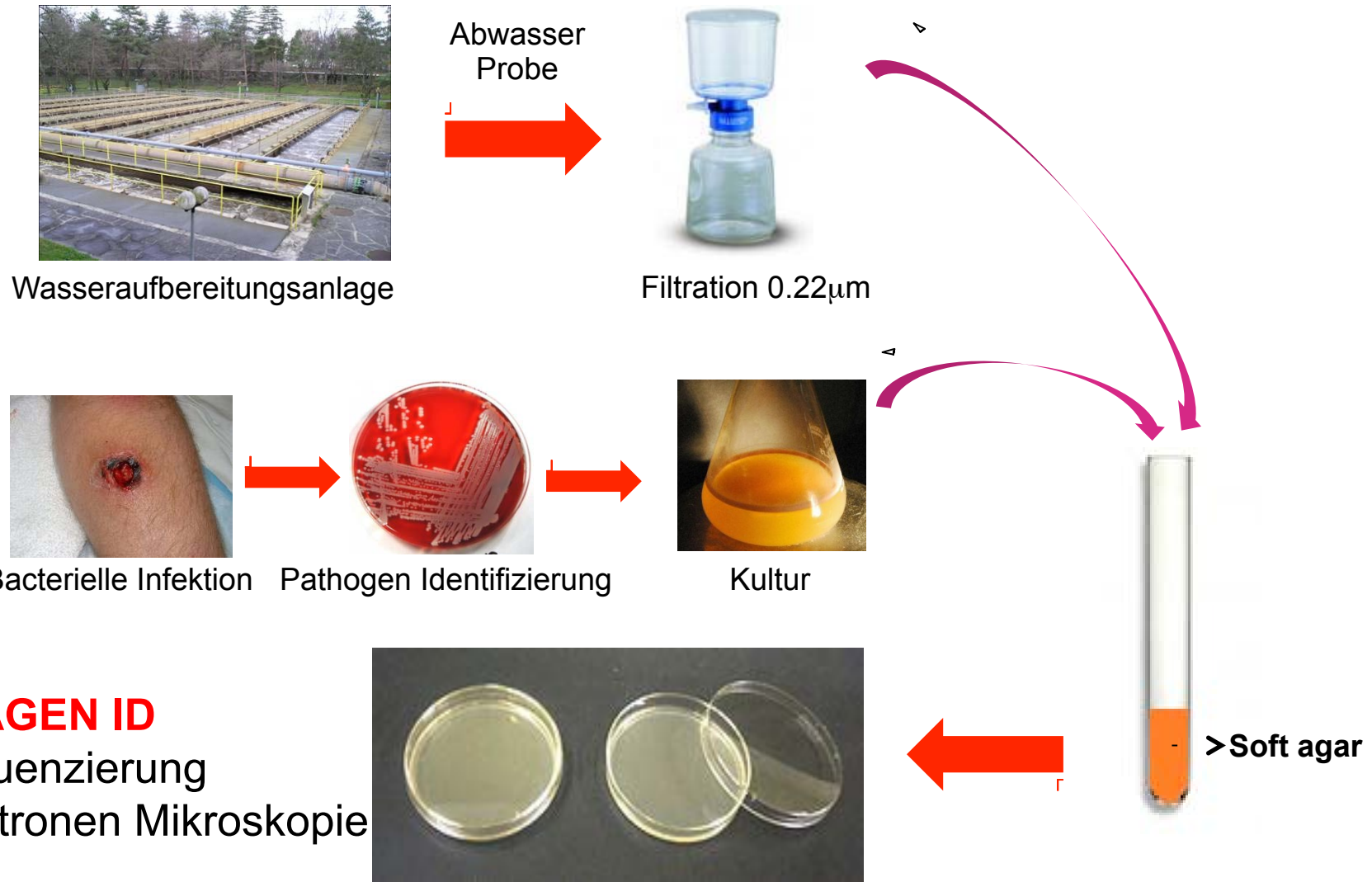


dsRNA



PHAGEN THERAPIE

Wie isoliert man Phagen ?

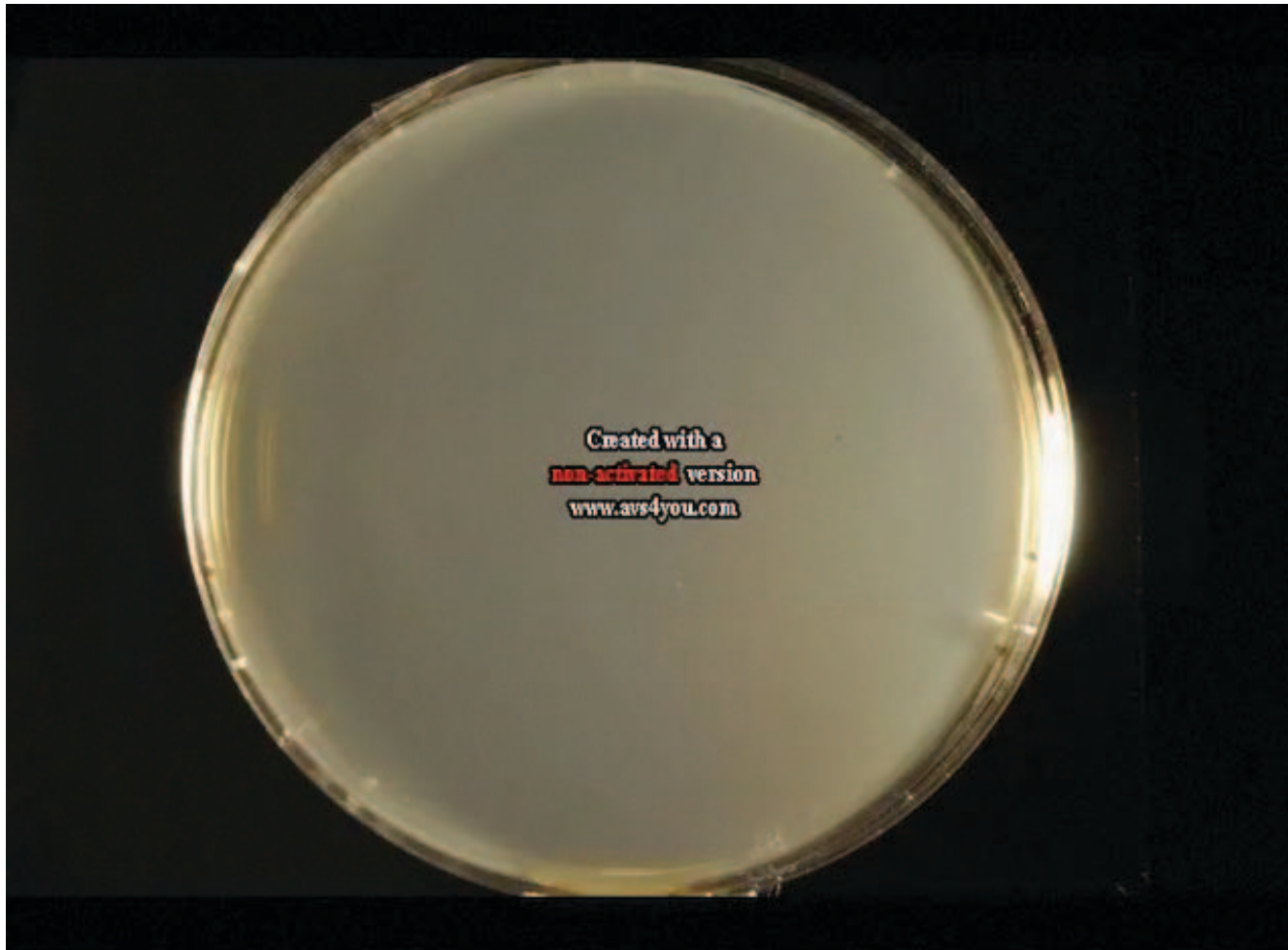


PHAGEN ID

Sequenzierung
Elektronen Mikroskopie

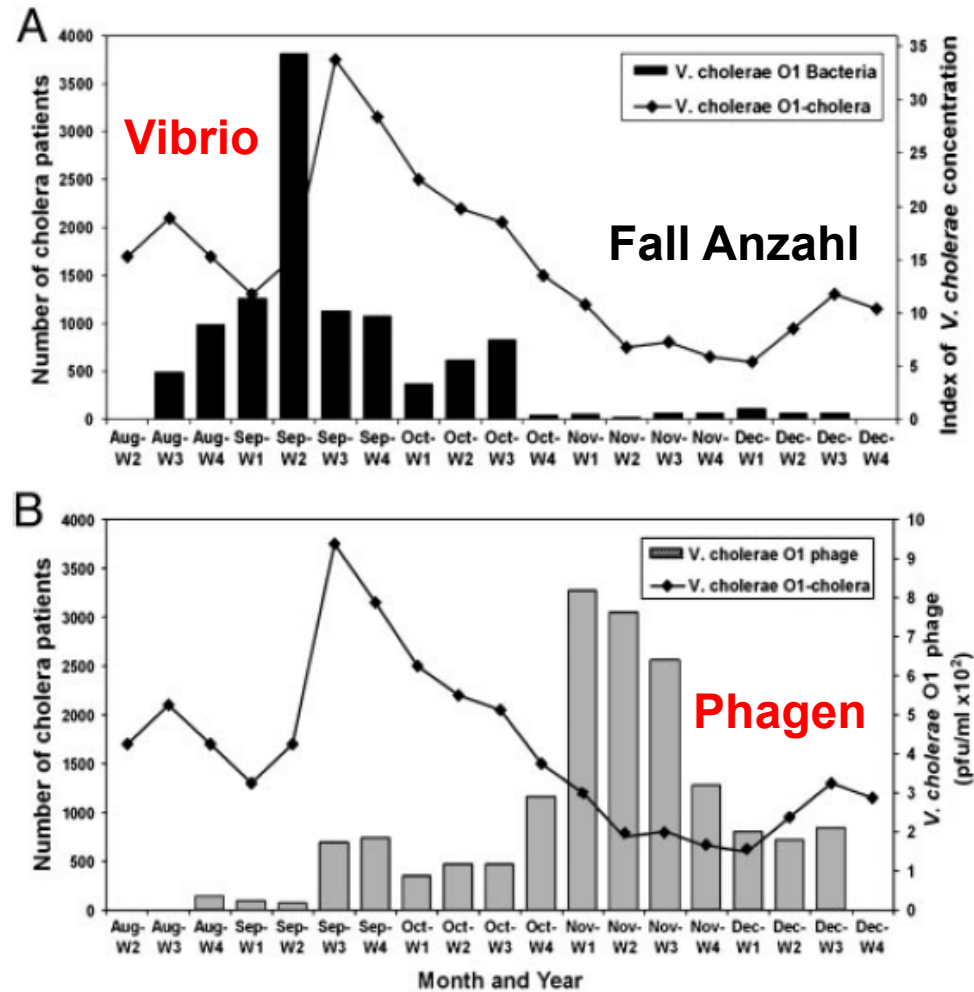
PHAGEN THERAPIE

Wie isoliert man Phagen ?



BAKTERIOPHAGEN POPULATIONSDYNAMIK

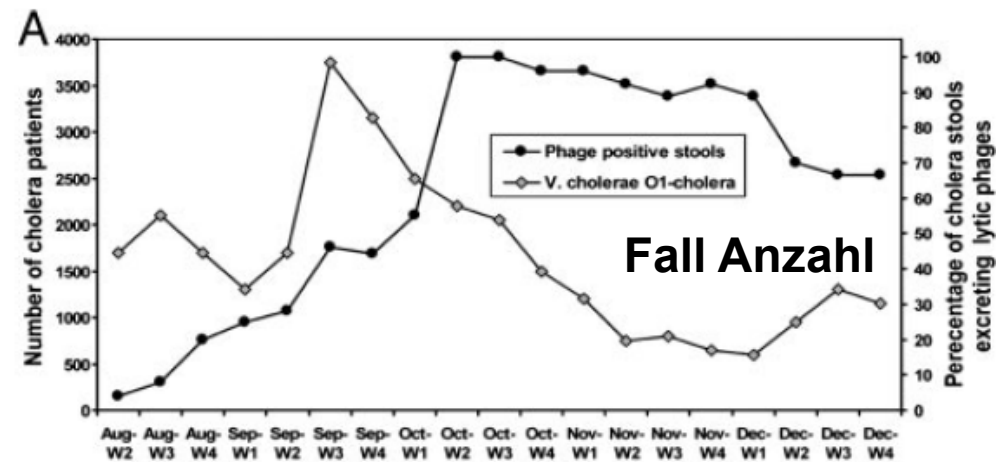
CO-EVOLUTION



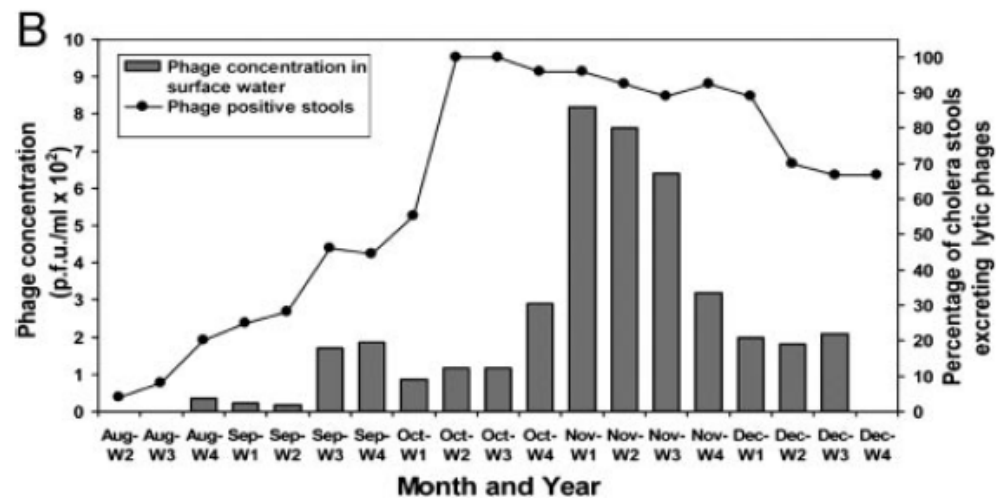
Faruque SM, PNAS, 2005 102 :6119–24

BAKTERIOPHAGEN POPULATIONSDYNAMIK

Phagen
In Fäkalien



Phagen
im Wasser

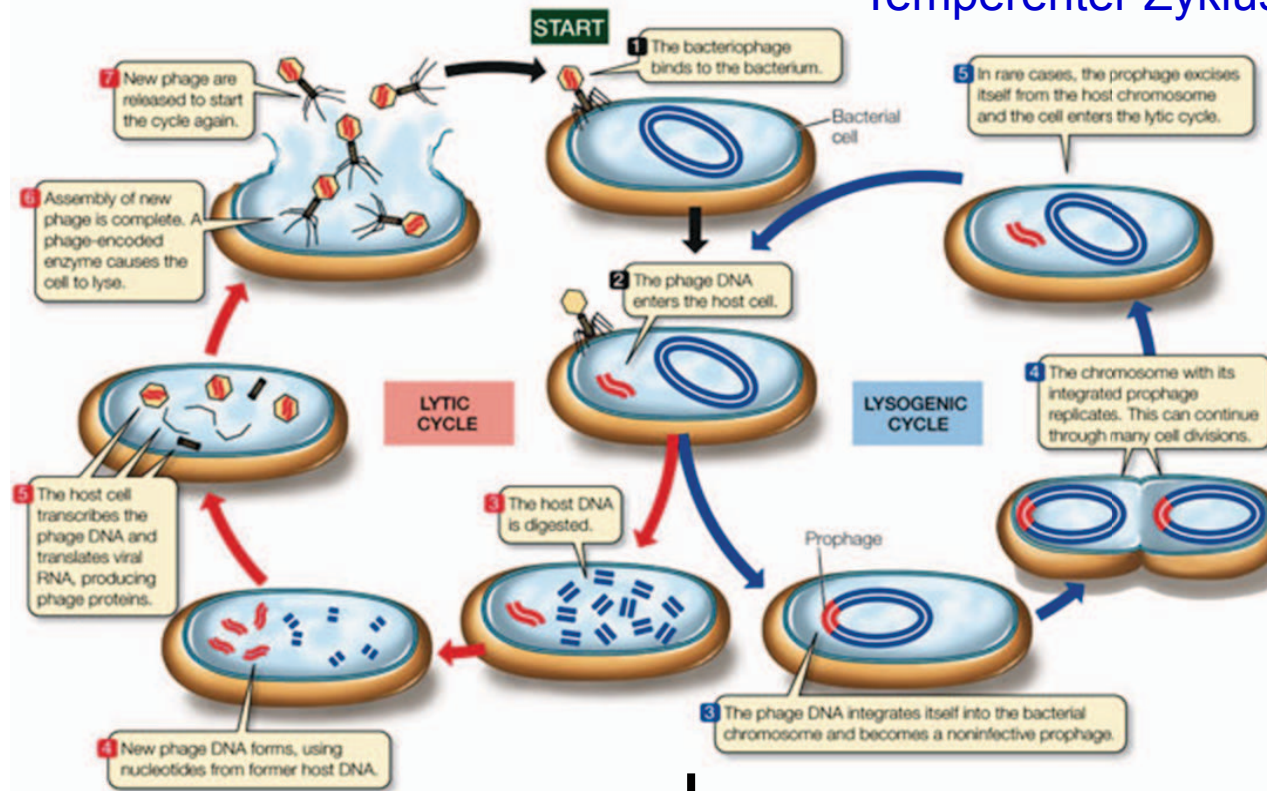


Faruque SM, PNAS, 2005 102 :6119–24

BAKTERIOPHAGEN LEBENSZYKLEN

Lytischer Zyklus

Lysogenie Temperenter Zyklus

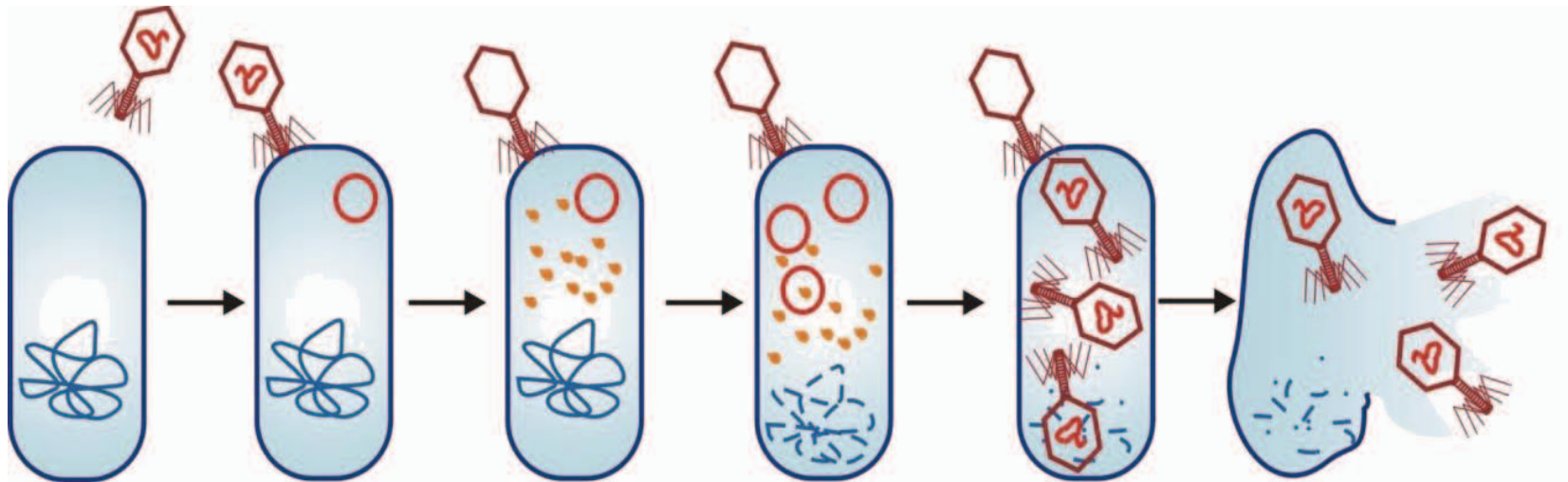


LIFE 8e, Figure 13.3

PHAGENTHERAPIE

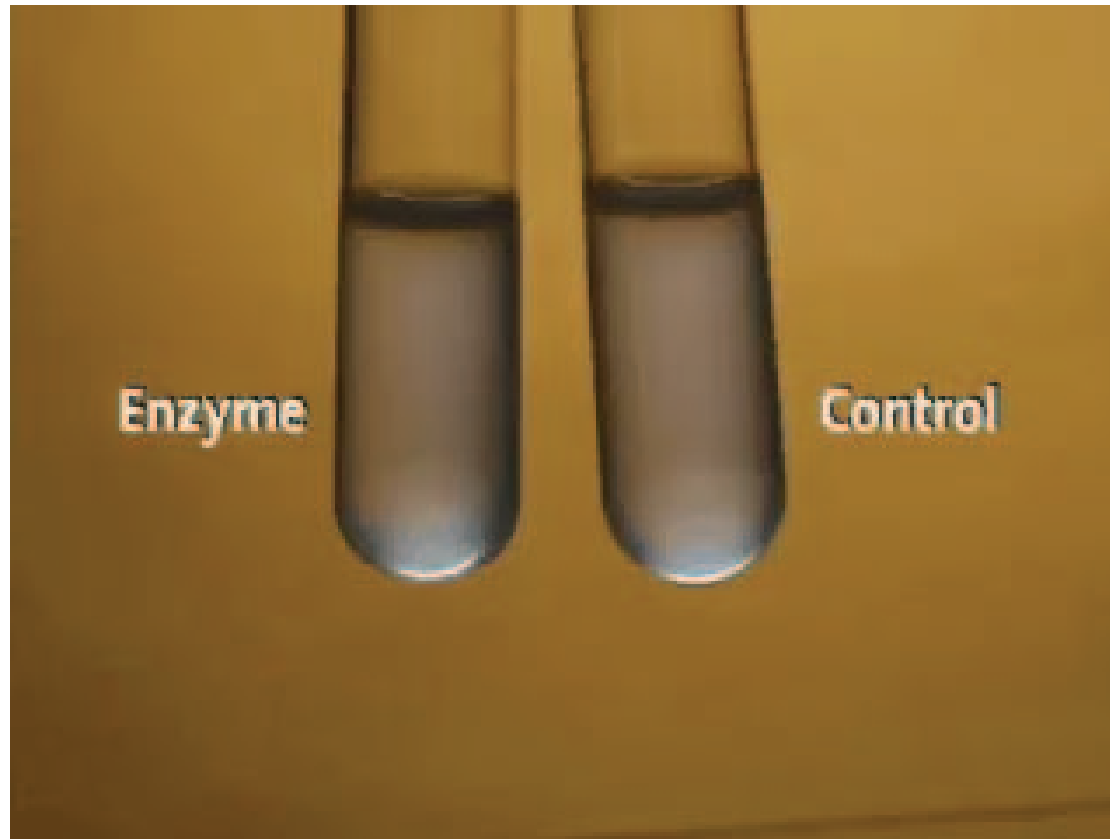
LYTISCHER ZYKLUS

Therapeutische Anwendung
von rein **lytische Phagen**
als antibakterielle Mittel



PHAGENTHERAPIE

LYTISCHER ZYKLUS





PHAGENTHERAPIE

GRUNDSÄTZE

- Bakterielle Viren
- Natürliche Raubtiere, die Bakterien fressen
- Unabhängig von AB Resistenz wirksam
- Phagen – Bakterien CO-Evolution

PHAGETHERAPIE - MENSCHEN

PHAGEN VERSUS ANTIBIOTIKA

PHAGEN

Sehr spezifisch
(nur wenige Stämme innerhalb
einer Bakterienart)

Entwicklung von neuen
Phagen: schnell und günstig

Schmales Spektrum:
Isolation der Bakterien nötig

Keine bekannte
Nebenwirkungen

ANTIBIOTIKA

Nicht/Kaum-spezifisch
(betreffen auch kommensale
Flora)

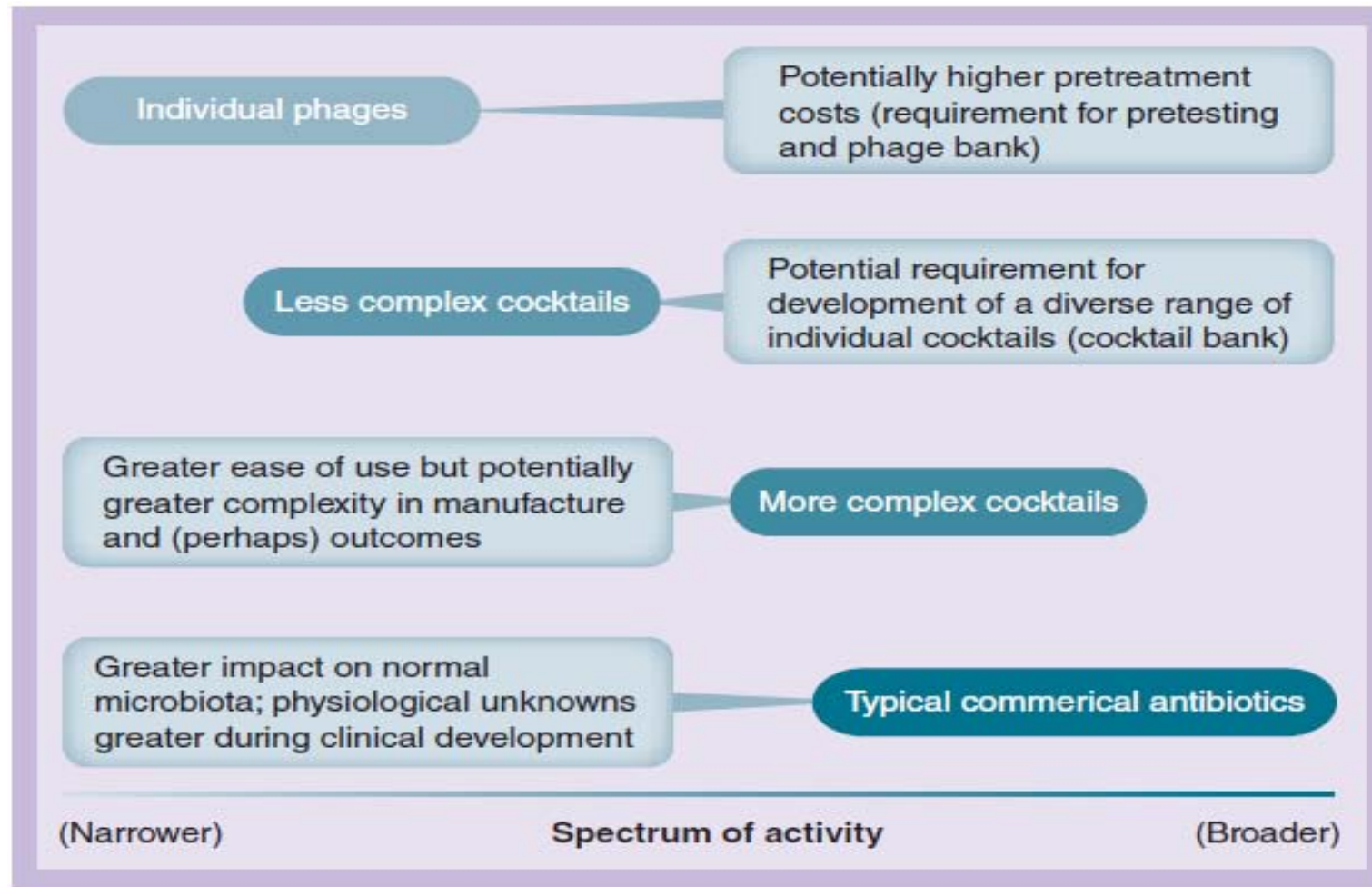
Entwicklung von neuen
Antibiotika: teuer und
zeitaufwendig

Breites Spektrum, keine
Isolation der Bakterien nötig

Mehrere Nebenwirkung
berichtet

PHAGETHERAPY

«SUR MESURE» VERSUS «PRÊT A PORTER»



PHAGENTHERAPIE

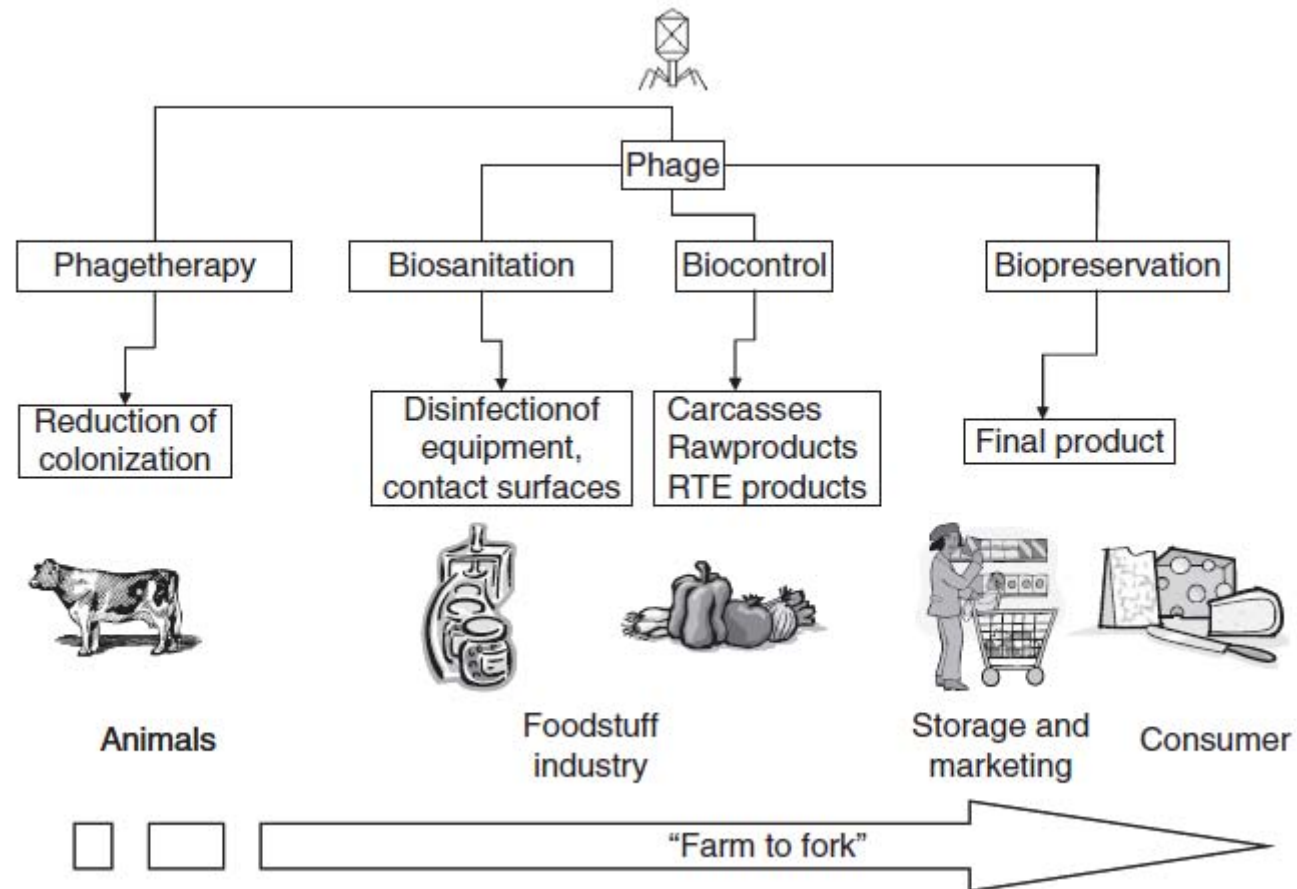
WELCHE PATIENTEN ?

Patienten mit komplexen Infektionen:

- (1) Multi-drug resistenten Keime
- (2) Patienten mit chronischen Infektionen
 - Zystische Fibrosis
 - Osteomyelitis
 - Chronische Ulcus
- (3) Katheter Infektionen bei dialysepflichtigen Patienten

PHAGENTHERAPIE

WO NOCH ? LEBENSMITTELINDUSTRIE



FORSCHUNG

PHAGOBURN 2013 - 2017



Phase I/II Randomized, multicentric, open label, standard of care controlled (silver sulfadiazine)

Objective:

Assess tolerance and efficacy of topical phagetherapy for burn wound infections due to *P. aeruginosa*

POPULATION:

Burn Patients

RESULTS :
June 2017



PHAGENTHERAPIE - SCHLUSSWORT

ONE HEALTH APPROACH

HUMANMEDIZIN

Innovative Behandlung bei selektionierten Patienten

VETERINÄRMEDIZIN

Chronische Wunden

LANDWIRTSCHAFT – LEBENSMITTELINDUSTRIE

Biologische Kontrolle bakterieller Infekte

UMWELT

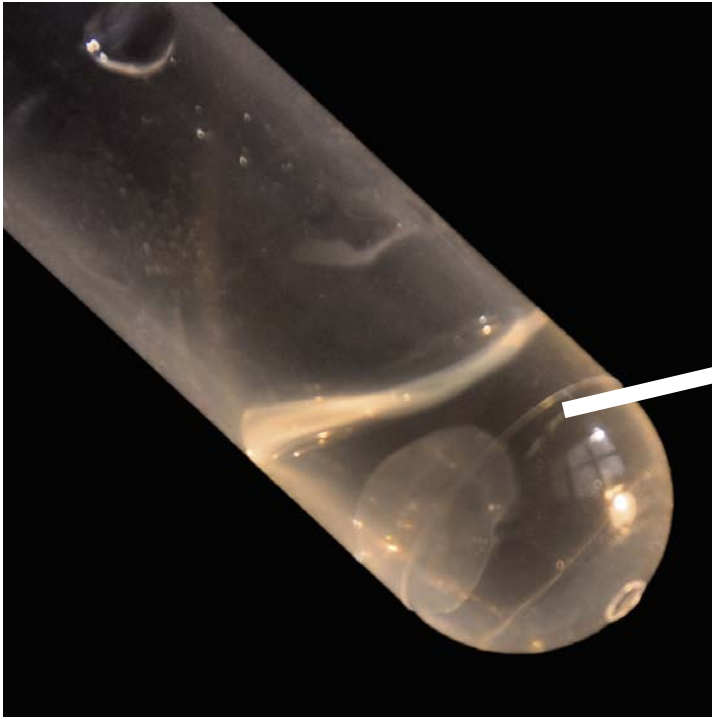
Einfluss der Phagentherapie auf die Umwelt



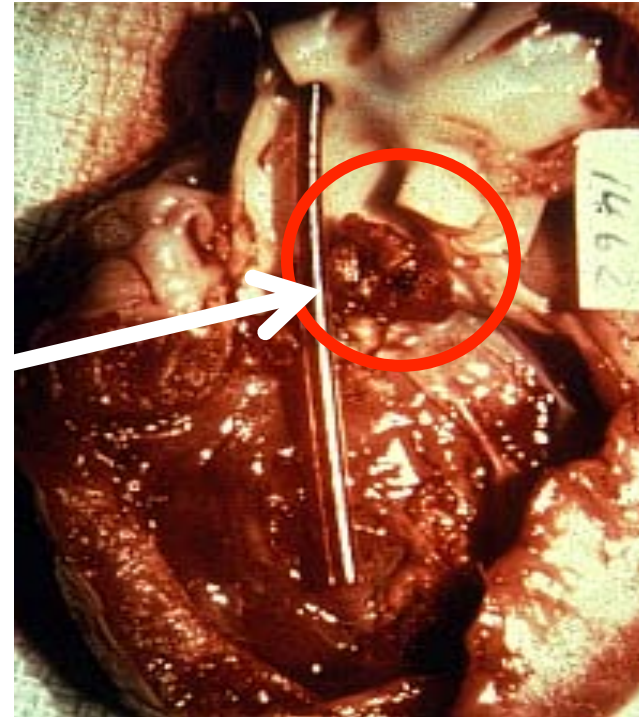
ANTI - *P. aeruginosa* PHAGE COCKTAIL

In vitro and in vivo evaluation in endocarditis model

***In vitro* Endocarditis Model
(Plasma-Fibrin Clot)**



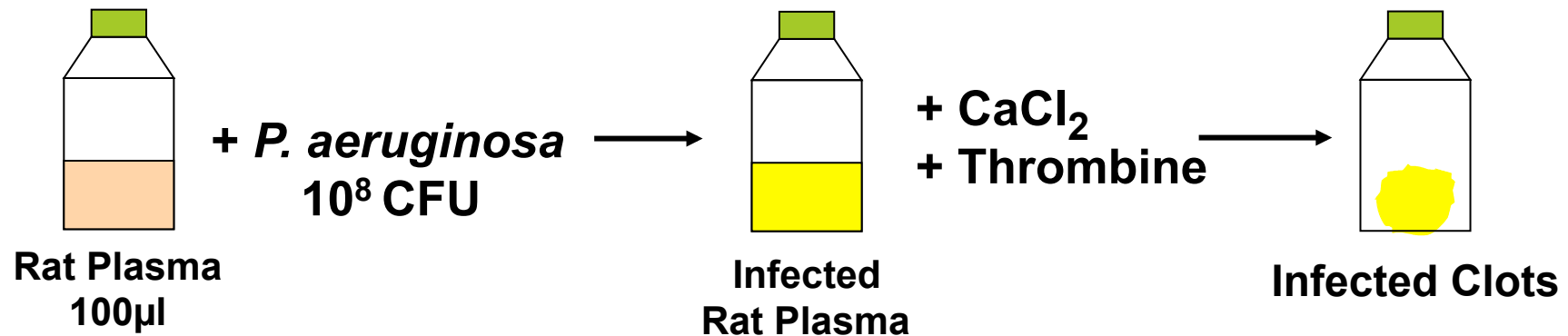
***In vivo* Endocarditis Model
(Plasma-Fibrin Vegetation)**





ANTI - *P. aeruginosa* PHAGE COCKTAIL

In vitro endocarditis model (Plasma-fibrin clot)

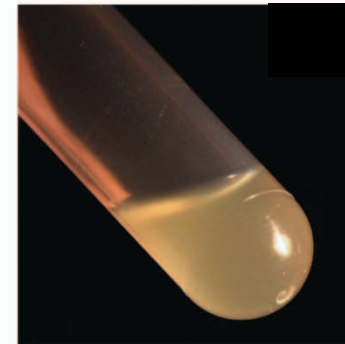
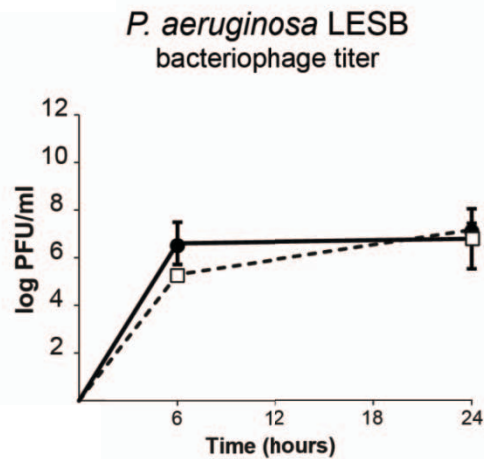
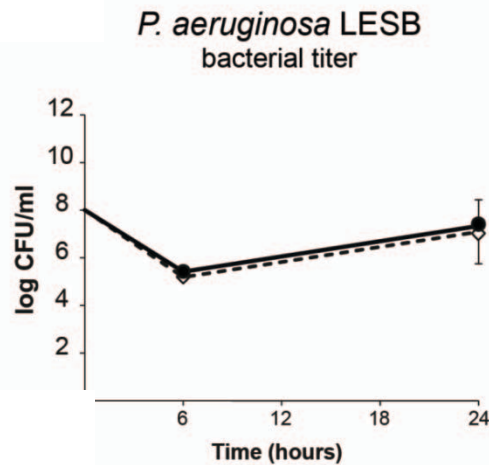


Incubation with cocktail
500μl 10⁸ PFU/ml

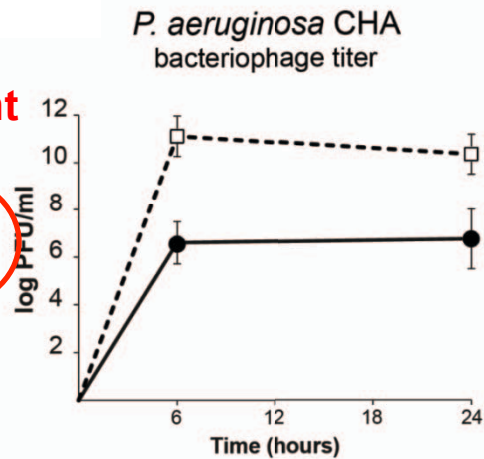
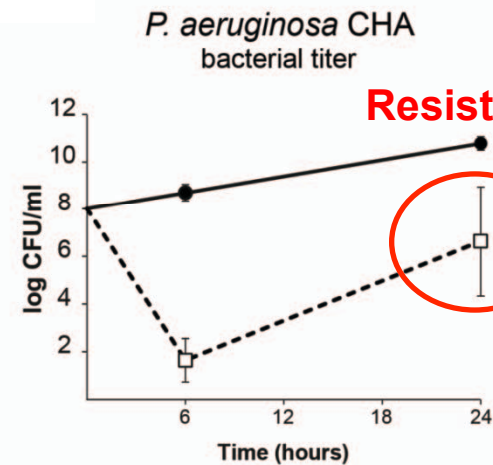


ANTI - *P. aeruginosa* PHAGE COCKTAIL

In vitro endocarditis model (Plasma-fibrin clot)



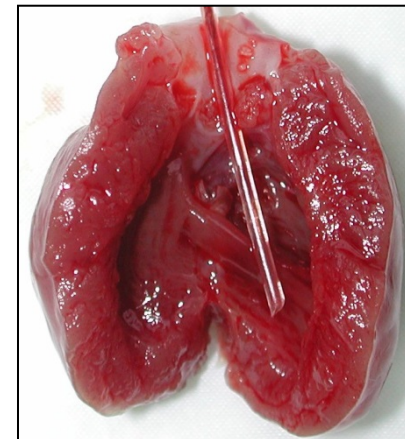
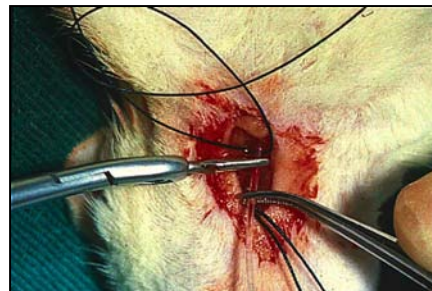
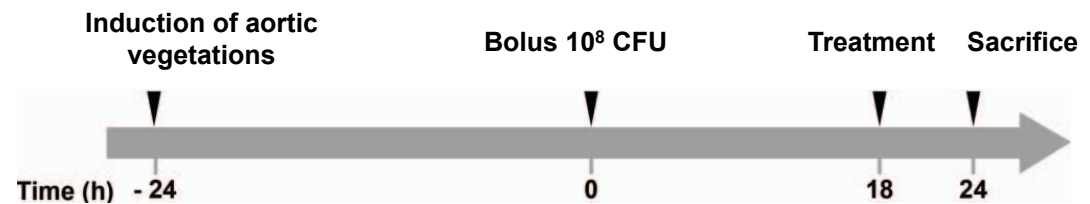
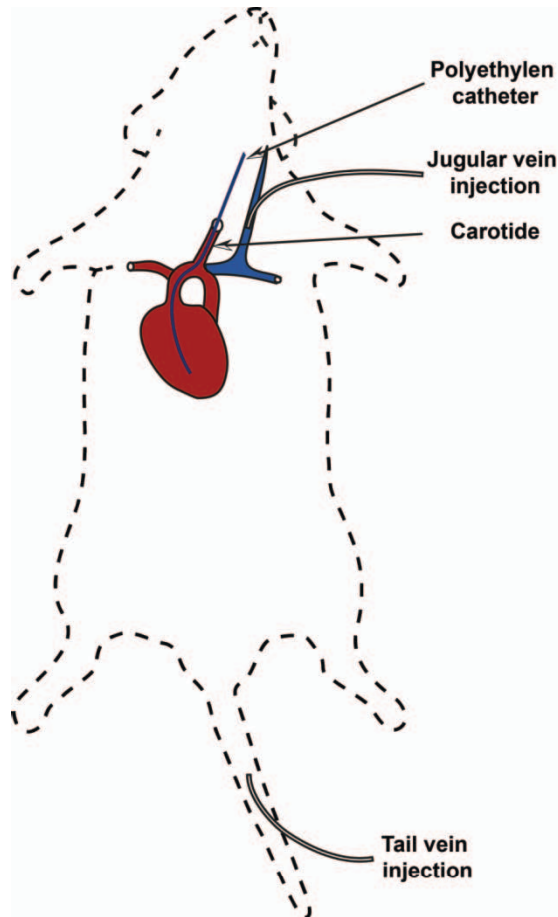
Control: Solid line
Phage Rx : dash line





ANTI - *P. aeruginosa* PHAGE COCKTAIL

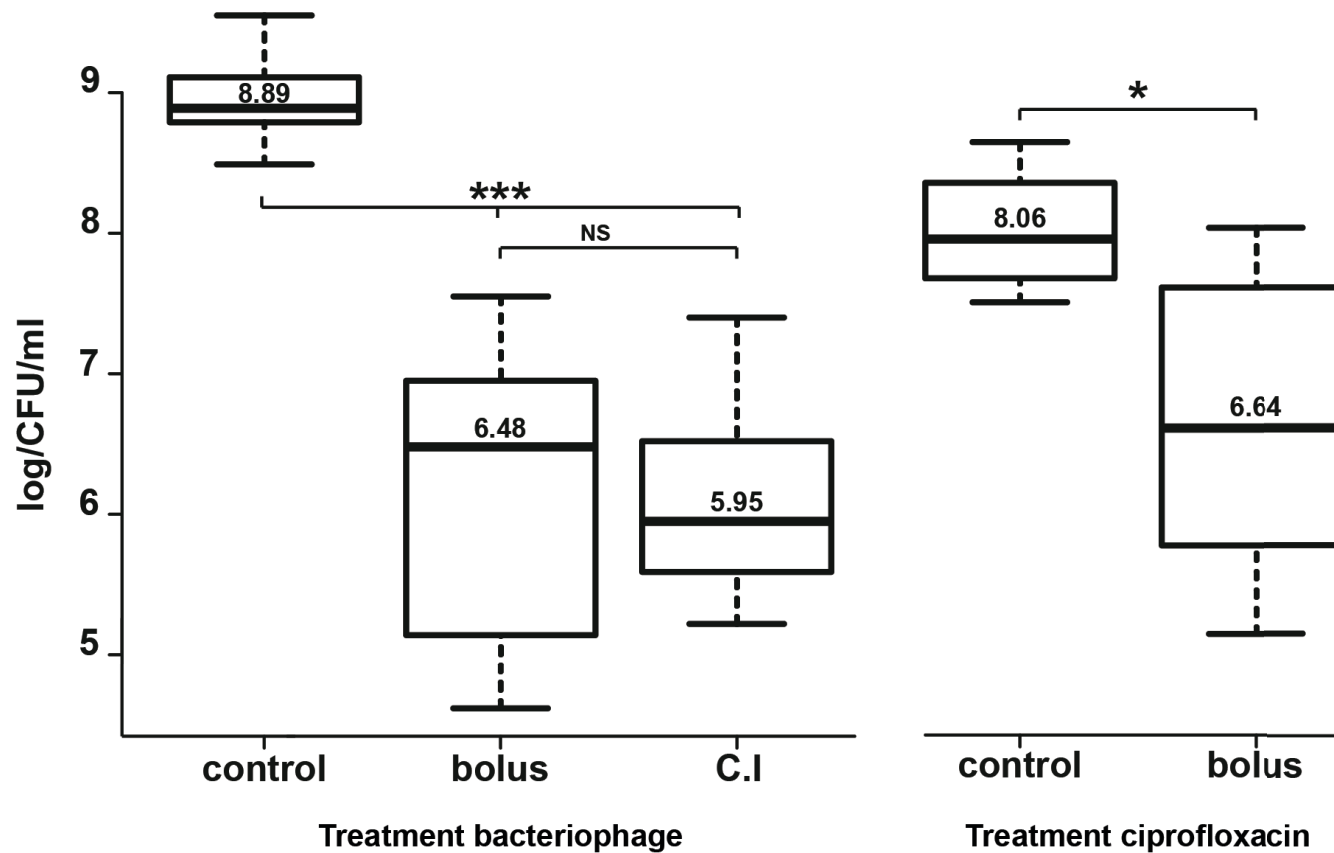
In vivo endocarditis model





ANTI - *P. aeruginosa* PHAGE COCKTAIL

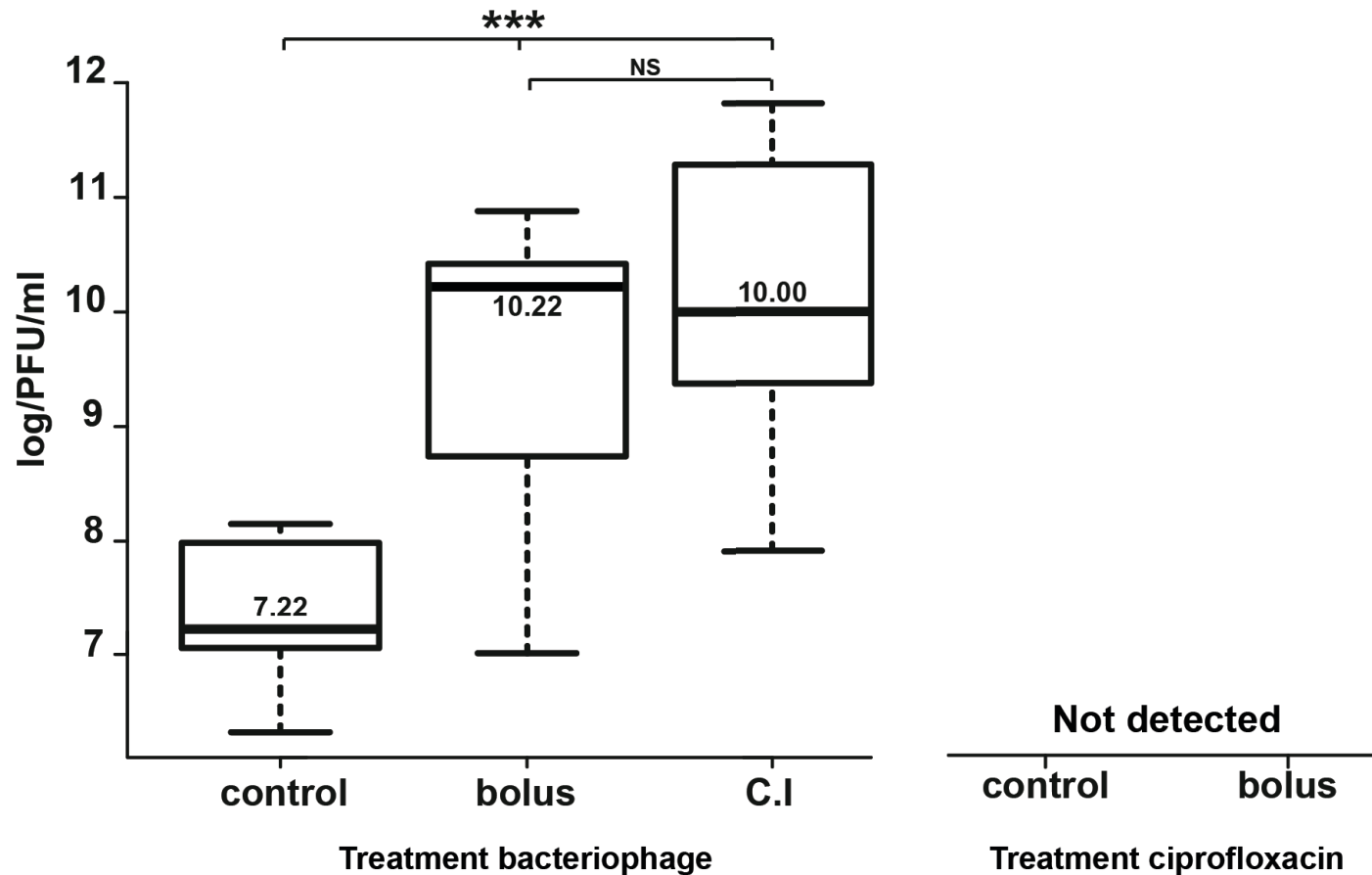
In vivo endocarditis model : Phage versus ciprofloxacin





ANTI - *P. aeruginosa* PHAGE COCKTAIL

In vivo endocarditis model : Phage titers in vegetations



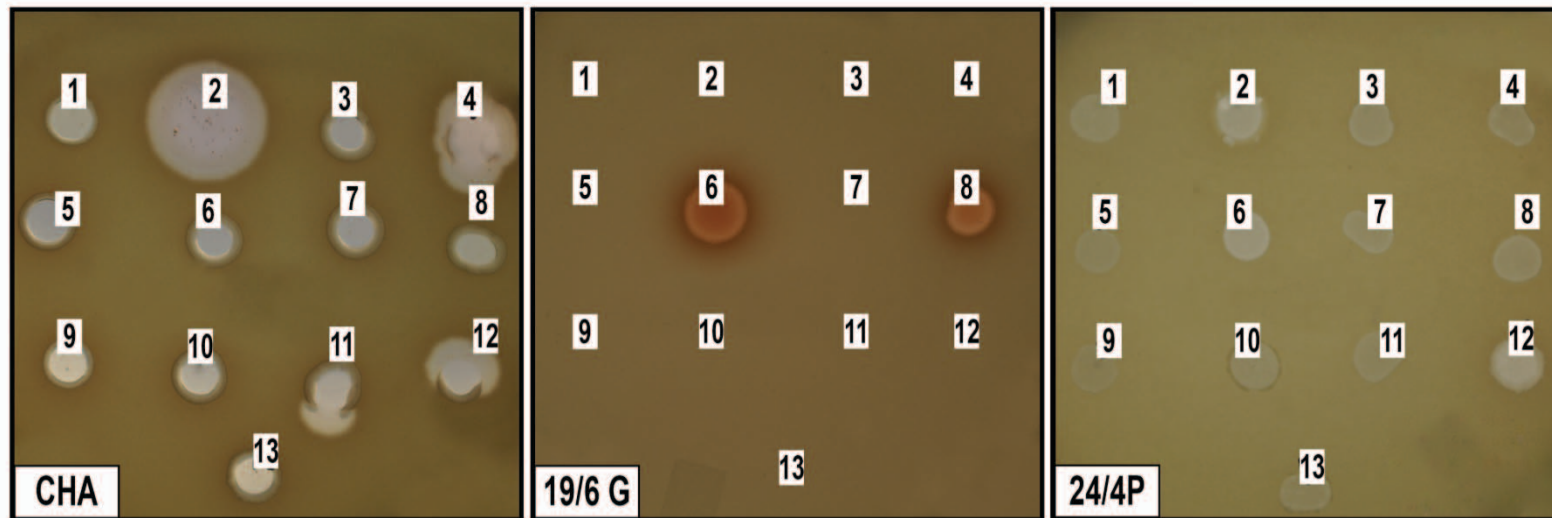


ANTI - *P. aeruginosa* PHAGE COCKTAIL

Analysis of resistant variants found *in vitro*

How to explain this difference in resistance development ?

Phenotype of Resistance



Wild Type

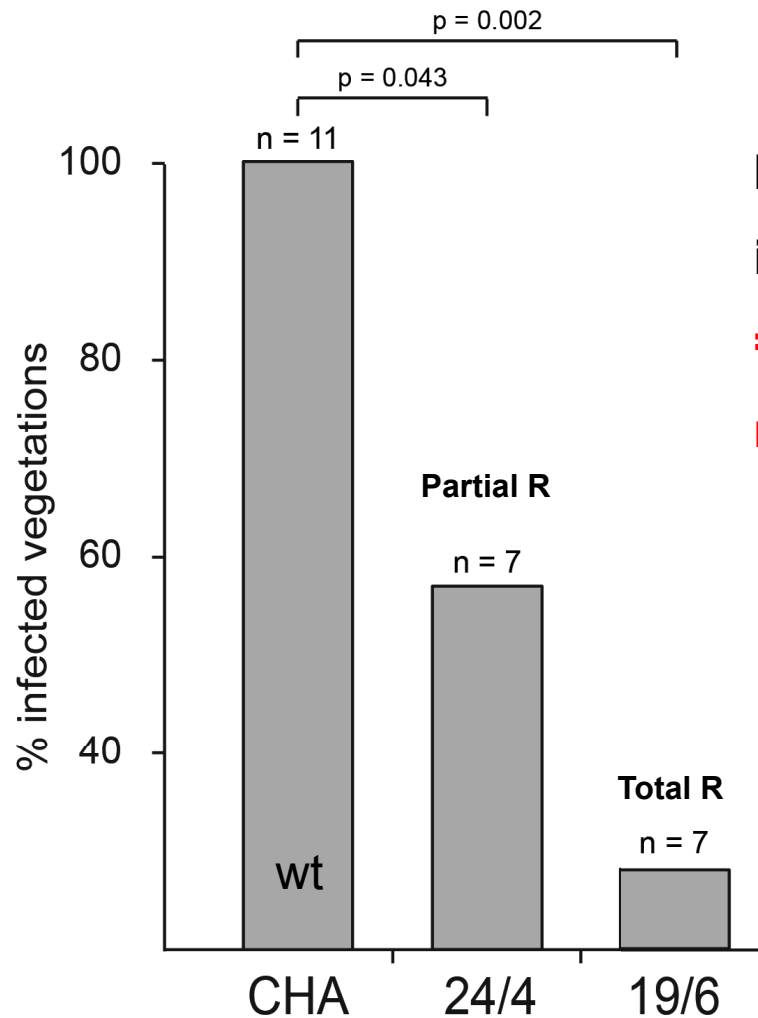
Resistant variant 1

Resistant variant 2



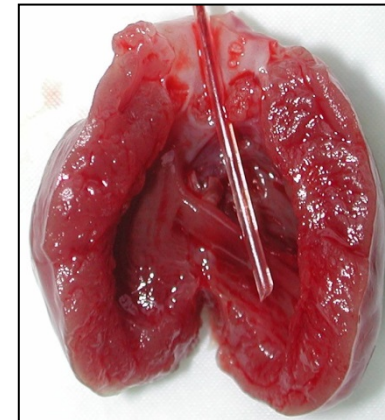
ANTI - *P. aeruginosa* PHAGE COCKTAIL

Evaluation of Infectivity of Resistant Variants



Infectivity in rats with catheter induced vegetations

=> Loss of infectivity for phage-resistant variants





ANTI - *P. aeruginosa* PHAGE COCKTAIL SUMMARY OF PRE-CLINICAL RESULTS

Phage efficacy requires phage amplification

Phage induced a rapid decrease of bacterial count in both the *in vitro* model of fibrin clot and in the rat model of endocarditis

Phage resistance develops *in vitro* but not *in vivo*

Resistant variants that developed *in vitro* lose infectivity *in vivo*