Phage Therapy: An alternative to antibiotics in the era of multi-drug resistance

Joint Graduate Seminar 2018

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SOVIET PSEUDOSCIENCE

- Phages are currently being used therapeutically to treat bacterial infections that do not respond to conventional antibiotics, particularly in Russia and Georgia.

- Thus called Soviet Pseudo Science by Western world

Presentation outline

Introduction to phage therapy

Milestones in phage history

Phage against clinically significant pathogens

Phage therapy vs antibiotic therapy

Problems

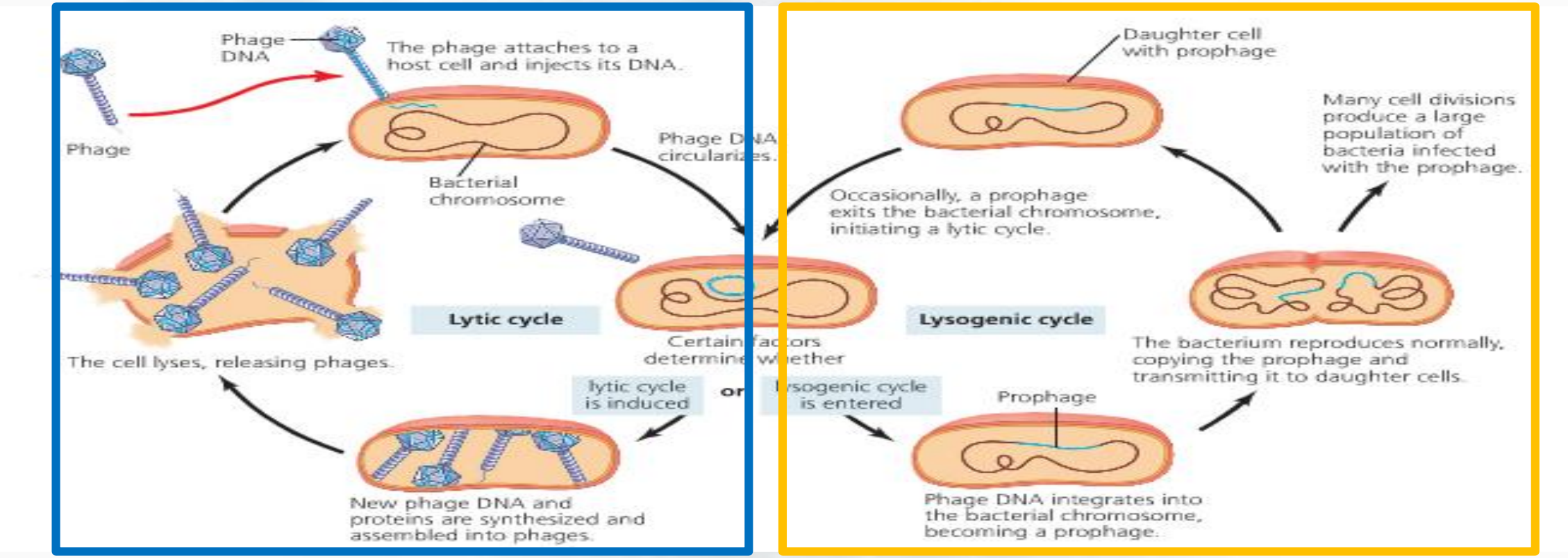
Conclusion

Introduction to phage therapy

Bacteriophages :

- Viruses that infect bacteria
- By injecting genetic materials
- Ubiquitous
- Obligatory parasites
- Self-limiting antibiotics for bacteria

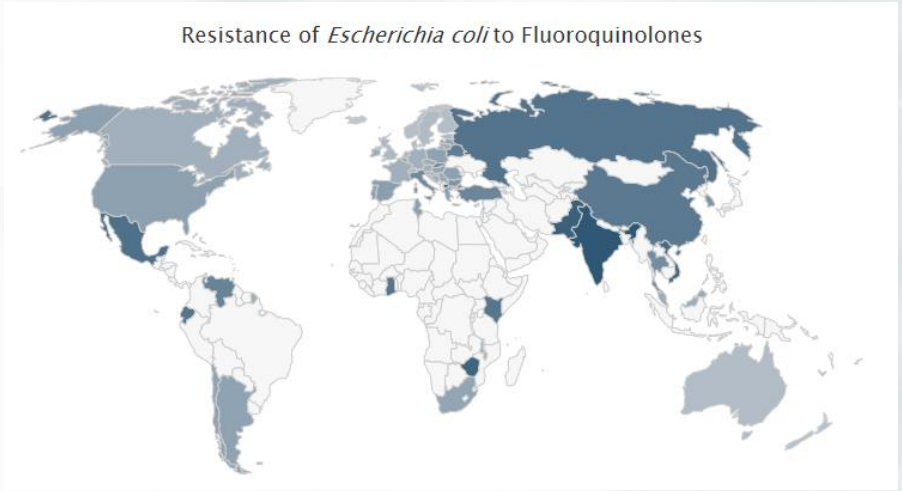
Phage Cycles

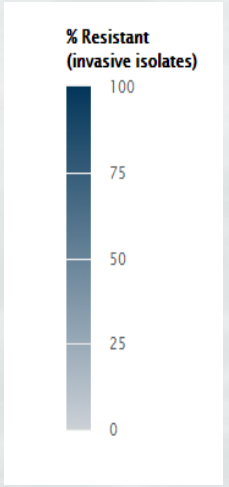


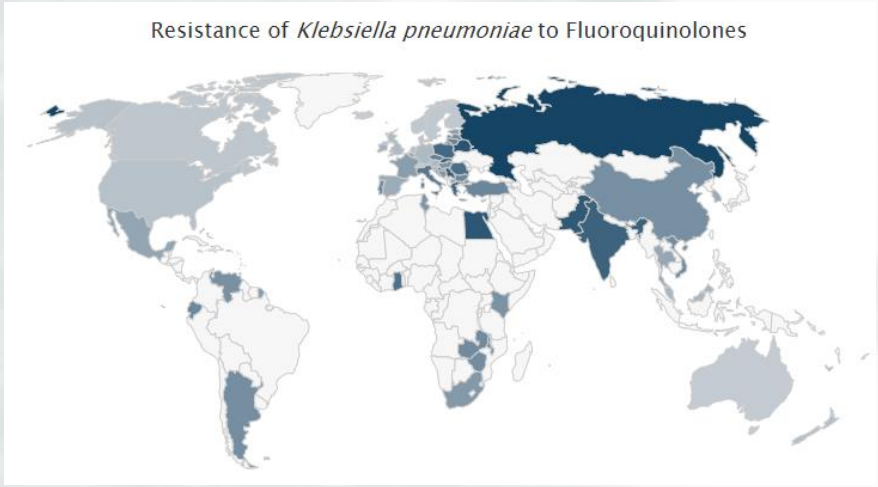
- Lytic phages instruct the machinery in the host cell to make more bacteriophages
- Lysogenic phages attach their strand of genetic instructions to the DNA of the bacteria. The phage DNA get replicated along with the bacterial generation by generation

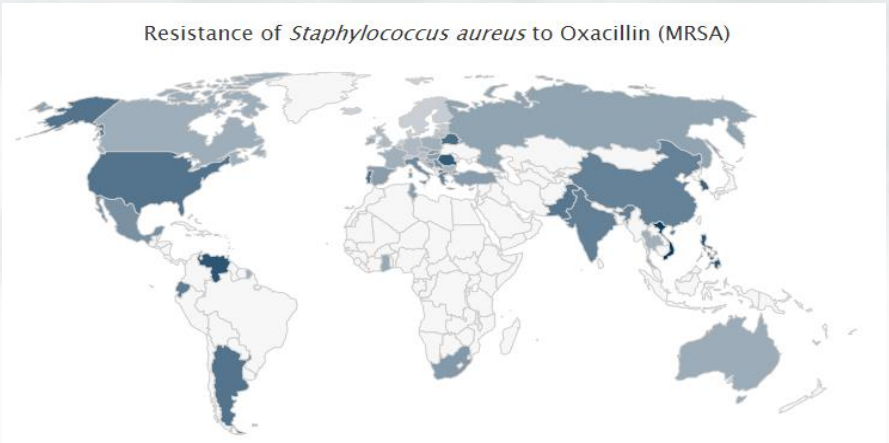
Antibiotic resistance:

- Over use and misuse
- MDR
- Need of alternative to conventional antibiotics



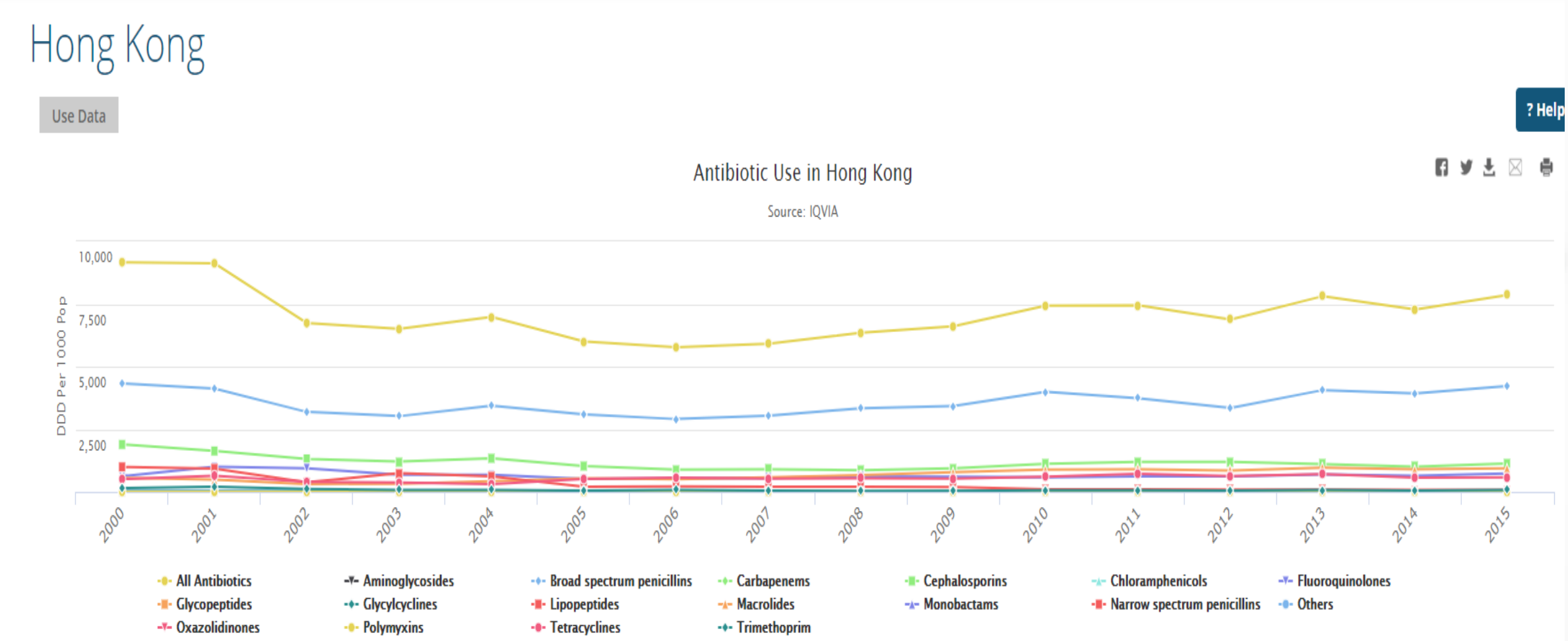






The Center for Disease Dynamics Economics & Policy. ResistanceMap: Antibiotic resistance. 2018. https://resistancemap.cddep.org/AntibioticResistance.php. Date accessed: May 31, 2018.

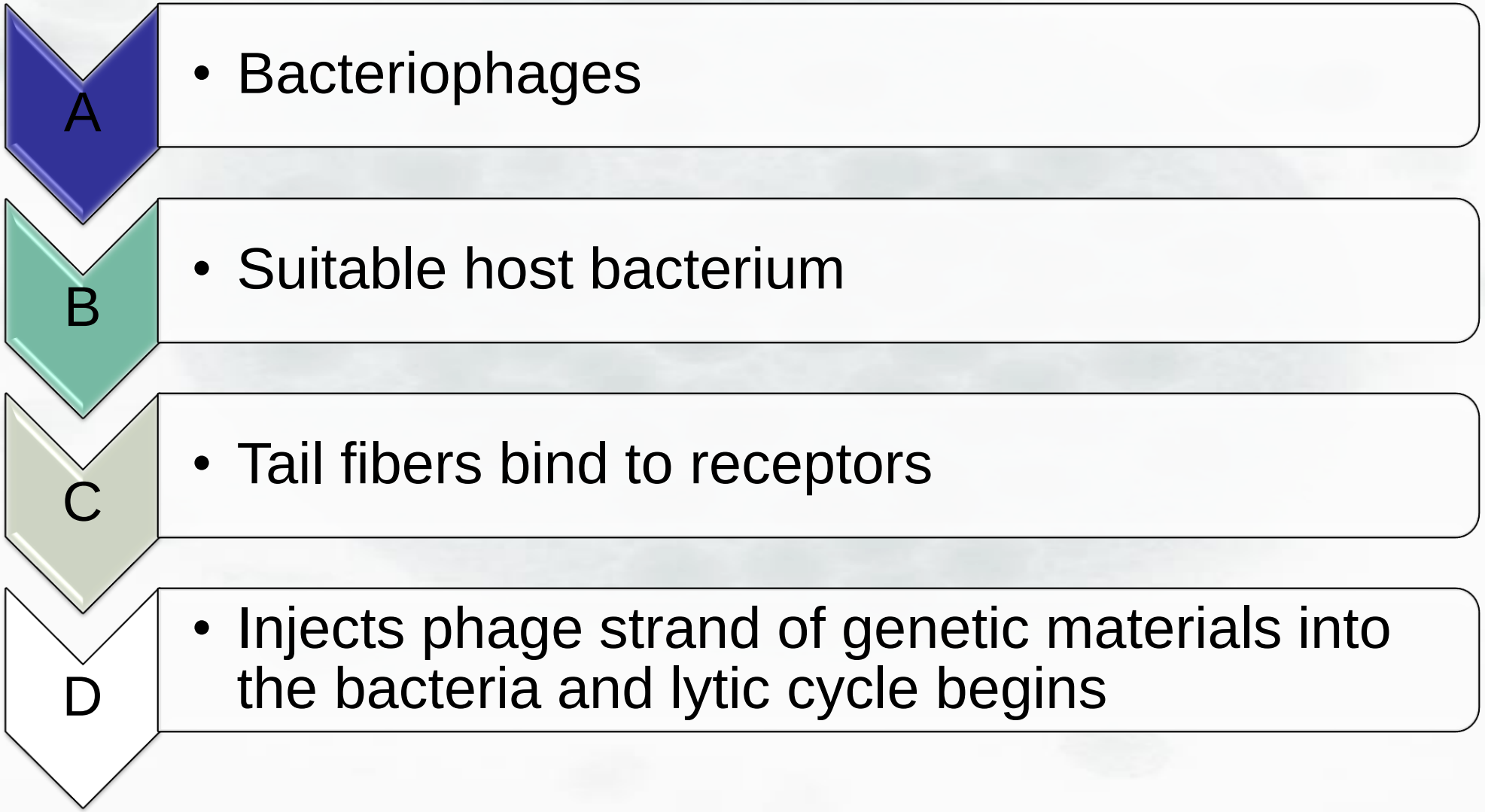
Antibiotic usage in Hong Kong for the year 2016



Phage therapy :

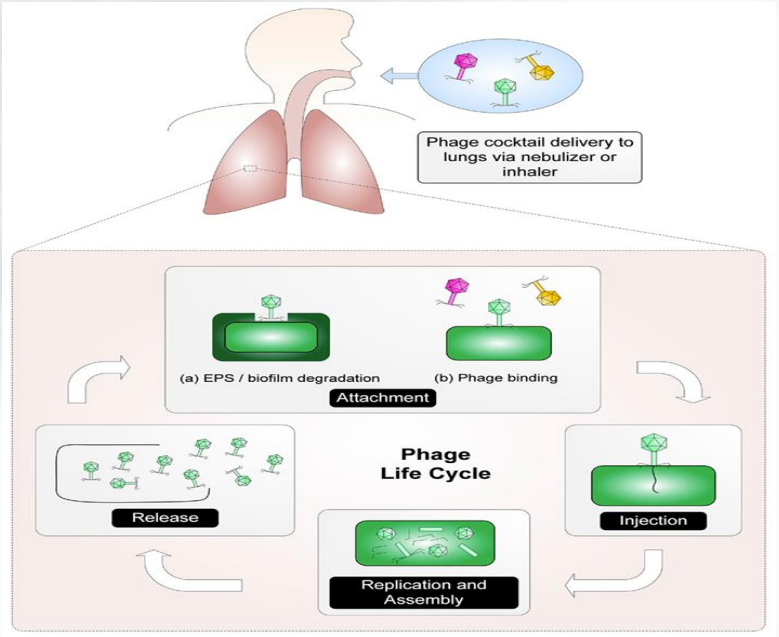
- An old idea re-emerging
- Involves the use of phages or their products as bio agents for the treatment or prophylaxis of bacterial infectious diseases
- Administration of phages
  - Orally through colon infusion
  - As aerosols
  - As injections (intradermal, intravascular, etc.)

Mechanism


A
• Bacteriophages
B
• Suitable host bacterium
C
• Tail fibers bind to receptors
D
• Injects phage strand of genetic materials into the bacteria and lytic cycle begins

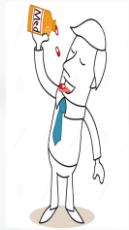
Approaches to bacteriophage therapy

1. Intact phage therapy
   - Whole phage products used
   - Problem ⟶ Resistance to phage attachment
   - Solution ⟶ Cocktail of phages & whole phage therapy
   - Other similar approaches
     - Use of whole phage as transport vehicles
   - Focus shifting to purifies phage components



2. Therapies based on phage components

- New window to anti-infective research
- Most promising phage components – LYSINS
- Purified phage-encoded peptidoglycan hydrolases
- Application
  - Bacillary dysentery
  - Infections in skin and nasal mucosa
  - Lung and plural infections
  - Inflammatory urological disease
  - Peritonitis
  - Post-surgical wound infections
  - Rhinitis and pharyngitis



On therapy…

A
- After specific trigger event in viral infection cycle

B
- Lysins translocate into bacterial cell wall

C
- Binds the major structural polymer-peptidoglycan

D
- Cleaves of bonds required for stability

E
- Hypotonic lysis

F
- PROGENY RELEASES

Milestones in phage therapy

Hankin observes antibacterial activity against *V.cholera* from Indian river water (1896)

D'Herell discovered and characterized the viral nature of phage (1917)

International bacteriophage Institute (1923)

Phages are used as tools for Mol.Bio. (1950s onwards)

Sequencing of phage genomes (1977 - onwards)

Fischetti demonstrate in vivo activity of phage lysins (2001)

BRED (2012 to present)

1890 1900 1920 1940 1960 1980 2000 2010 2018

Gamaleya confirms Hankin's observation with *Bacillus subtilis* (1898)

Twort observes the antibacterial activity of phage in *Staphylococcus aureus* (1915)

Isolation of phage λ (1951)

Work of Smith and Huggins revitalizes phage research in west (1980s)

FDA approval to use phage cocktail in ready-to-eat meat to prevent *Listeria* contamination (2006)

Phage against clinically significant pathogens

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PMCID: PMC5515400
PMID: 28719657

Isolation and *in vitro* evaluation of bacteriophages against MDR-bacterial isolates from septic wound infections

Roja Rani Pallavali,[1] Vijaya Lakshmi Degati,[1] Dakshayani Lomada,[2,¤a] Madhava C. Reddy,[3,¤b] and Vijaya Raghava Prasad Durbaka[1,*]

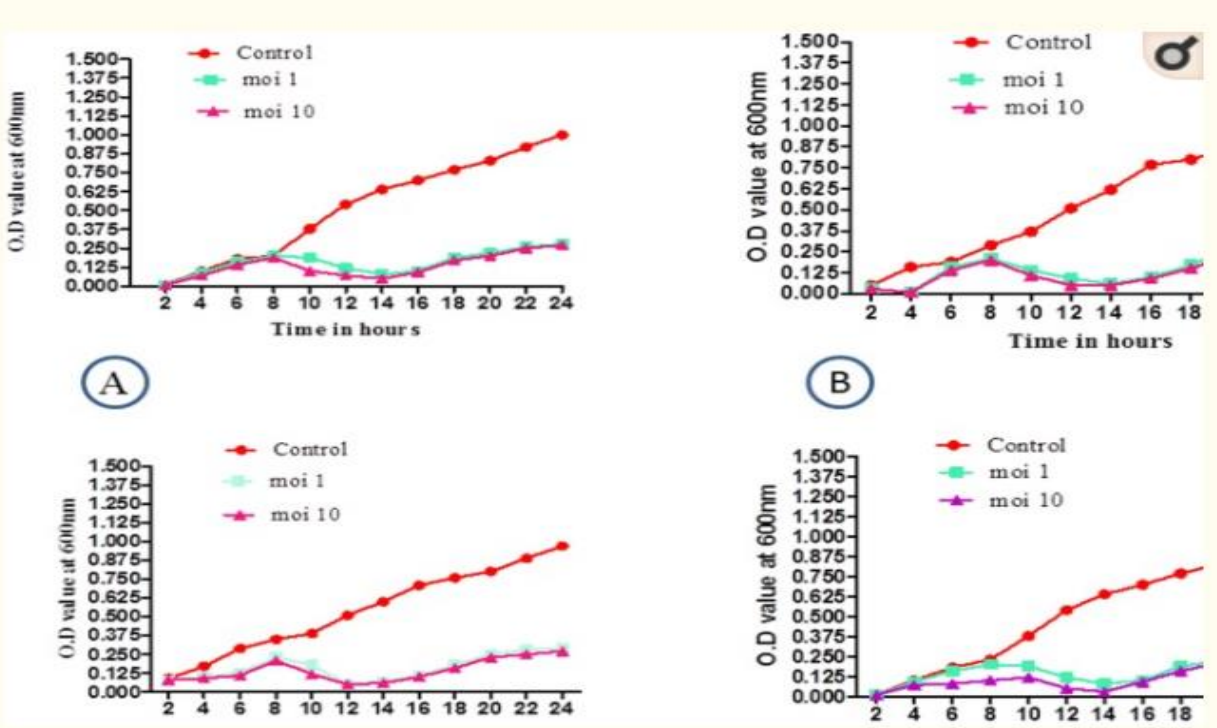


Fig 5

Effect of bacteriophages on the respective bacteria *in vitro*.

Reduction of bacterial growth by corresponding phages compared with control. A. MDR-KP1 (control), phage KP DP1 at m.o.i 1 and 10 (test). B. MDR-SA1 (control), phage SA DP1 at m.o.i 1.

- A total of 130 septic wound isolates
- 80 isolates were MDR
- 86% Gram negatives – MDR
- 100% Gram positives – MDR
- Bacteriophages - PA DP4, SA DP1, KP DP1, and EC DP3

- MDR-gram-positive bacteria and gram-negative obtained from septic wounds were susceptible to bacteriophage lysis

- Results suggest that these bacteriophages could be potential therapeutic options for treating septic wounds caused by *P. aeruginosa*, *S. aureus*, *K. pneumoniae* and *E. coli*

Summary of Clinical Phage Therapy of Pulmonary Infections

Reference	Year	Treatment of…	Etiology	Delivery	Efficacy[a] (# cases)
Morrison and Gardner[26]	1936	Bronchial fistula	"a colon bacillus"	Topical	100% (1)
Shishenko[28]	1938	Newborns and infants	*Staphylococcus* (other?)	Topical	[b]
Cevey and Schwiez[29]	1958	Pleuropulmonary perforation-associated pleural empyema	*Staphylococcus*	Topical	100% (1)
Delacoste[33]	1959	Refractory coughs	N.A.[c]	Inhalation	100% (19)[d]
Hoeflmayr[9]	1962	Bronchitis	Streptococci (2/3); Staphylococci (1/3)	Inhalation	90% (29)
Garsevanishvili[34]	1974	Pneumonia	Staphylococci, streptococci, and enterics were targeted	Inhalation	[e] (189)
Nikolaeva[35]	1974	Lung infection and pneumonia	Staphylococci	Inhalation	[f]
Sakandelidze and Meipariani[36]	1974	Lung abscesses and bronchiectasis	*Staphylococcus aureus, Proteus*, and Streptococci	Subcutaneous or topical	92%
Ioseliani *et al.*[38]	1980	Lung infections	Staphylococci and/or others	Inhalation, topical[g]	>90% (45)
Meladze *et al.*[40]	1982	Parenchyma and pleura infections	*Staphylococcus*	Inhalation, topical, parenteral	>90% (223)
Chkhetia[41]	1984	Recovery from lung operations	N.A.	Topical, parenteral	>90% (107)[h]
Clinical Trials[27]	1985	Various lung infections	N.A.	N.A.	77% (60); 90% (61)[i]
Slopek *et al.*[42]	1987	Various lung infections	*Escherichia, Klebsiella, Proteus, Pseudomonas, Staphylococcus*, and *Streptococcus*	Topical, *per os*	87% (202)
Weber-Dabrowska *et al.*[47]	2000	Various lung infections	*E. coli, Klebsiella, Proteus, Pseudomonas, S. aureus*	Topical, *per os*	>90% (376)
Kvachadze *et al.*[32]	2011	Cystic fibrosis-associated infections	*Staphylococcus* and *Pseudomonas*	Inhalation	[j]

[a]Approximately equivalent to percentage "++" or higher as found in Figure 2 through **Figure 5**.
[b]At least one apparent success of 3 cases of pleuritis.
[c]Information not available.
[d]No total failures.
[e]Degree of success is not easily discerned from the publication of this study.
[f]There was "general improvement in the condition" in treatment of lung abscesses.
[g]"Applying bacteriophage with antibiotics by inhalation, catheterization, bronchoscopy and to the pleural cavity…" (p. 66)
[h]Phages in combination with antibiotics versus 80% (45) for antibiotic treatment alone.
[i]Phage treatment along ("ISVP") versus phages plus antibiotics ("ISVP + ABP"), respectively.
[j]50% reduction in required ongoing antibiotic treatment.

(2015). Phage therapy of pulmonary infections. Bacteriophage, 5(1), e1020260. doi:10.1080/21597081.2015.1020260

She drank live viruses for two weeks. It worked

Case Report 1

Anna Kuchment and Bianca Castro

Now Swearingen's medical records confirm the outcome: She is cured.

Patti Swearingen, of Rowlett, poses for a portrait at her home on June 15. Swearingen used a bacteriophage to treat her antibiotic-resistant infection that she had for six years. (Carly Geraci/Staff Photographer)

- MDR *Klebsiella pneumoniae*
- March 2018
- They flew 6,500 miles to a small clinic in Tbilisi, Georgia
- Doctors had her drink live viruses twice a day for two weeks

https://www.dallasnews.com/news/science-medicine/2018/06/21/cured-virus-rowlett-woman-receives-experimental-treatment-debilitating-infection

This Scientist Used Live Viruses To Save A Woman's Life From A Superbug Infection

Once dismissed as fringe, phage therapy is gaining traction as a last resort when antibiotics fail. It's the subject of a new episode of the Netflix docuseries *Follow This*.

Azeen Ghorayshi
BuzzFeed News Reporter

"I wasn't released because I was better — I was released because nothing was working," Rogers, now 23, told BuzzFeed News.

Paige Rogers

Benjamin Chan and Paige Rogers.
Paige Rogers

Case Report 2

- MDR *Pseudomonas aeruginosa*
- In 2017
- In Texas
- Inhalation of cocktail of phages for few months

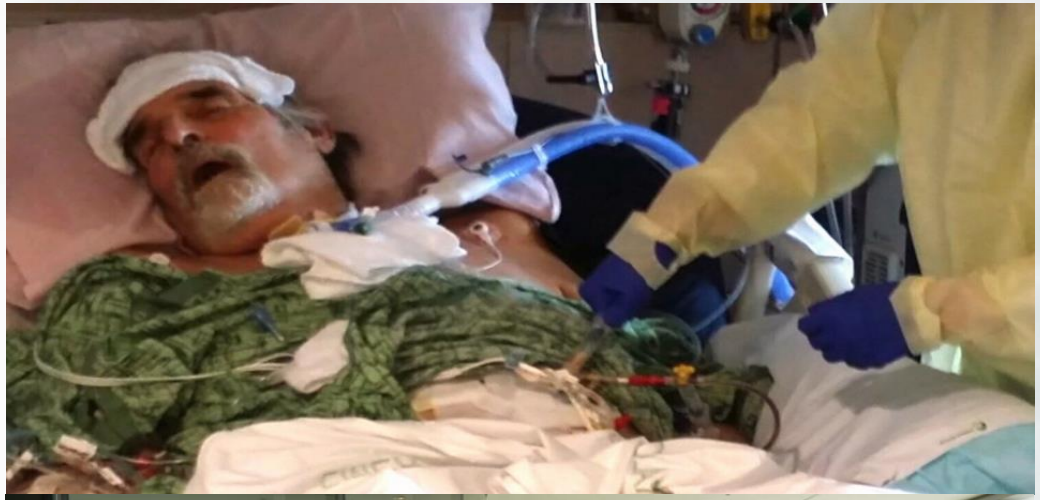
https://www.buzzfeednews.com/article/azeenghorayshi/phage-therapy-follow-this

Novel Phage Therapy Saves Patient with Multidrug-Resistant Bacterial Infection

Intravenous viruses are used to target deadly bacterium; dramatic case suggests potential alternative to failing antibiotics

April 25, 2017 | Scott LaFee and Heather Buschman, PhD

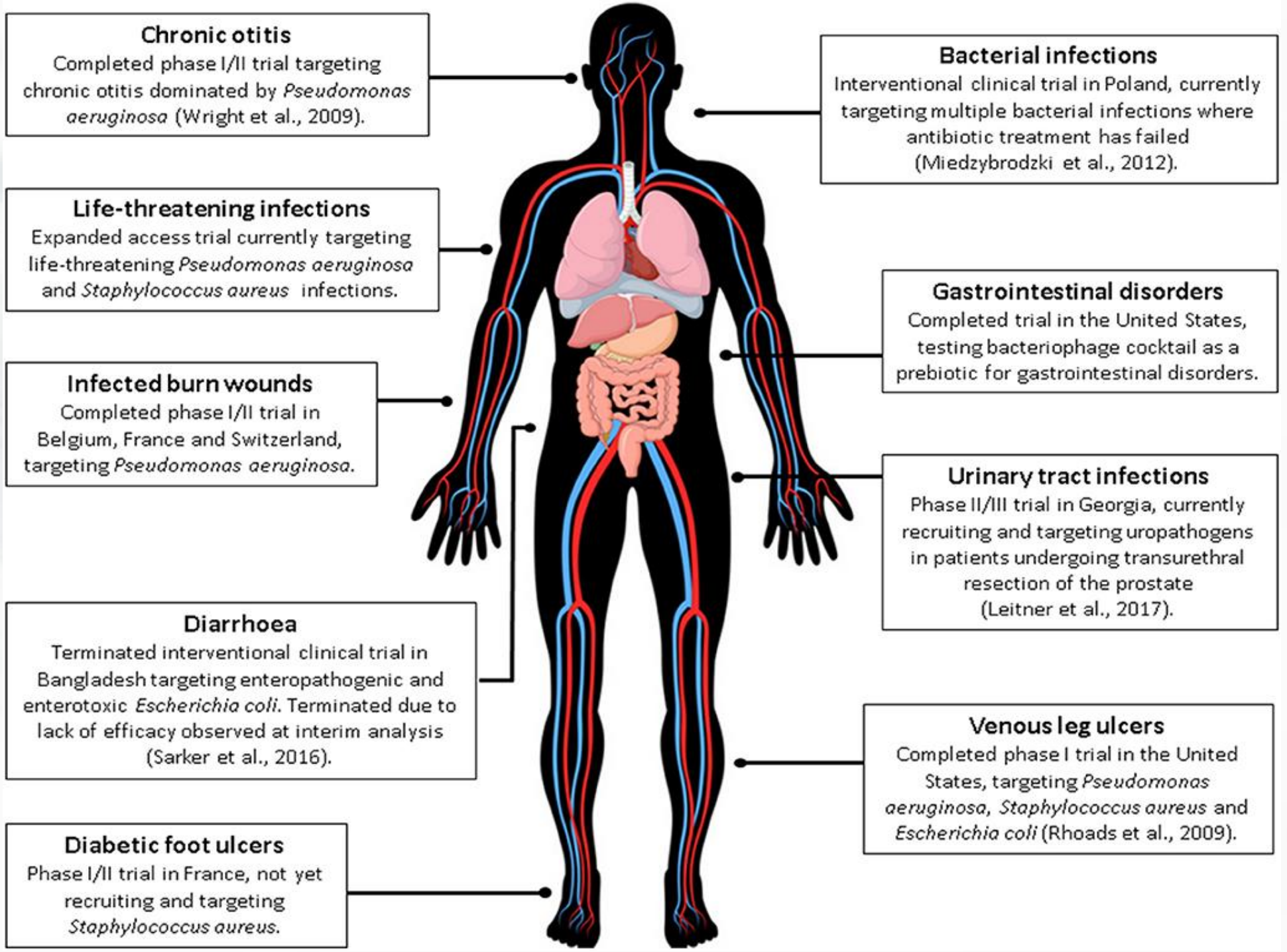
Case Report 3



- MDR *Acinetobacter baumannii* **“Iraqibacter”**
- June 2016
- University of California-San Diego’s medical center
- Woke up from a coma and fully recovered

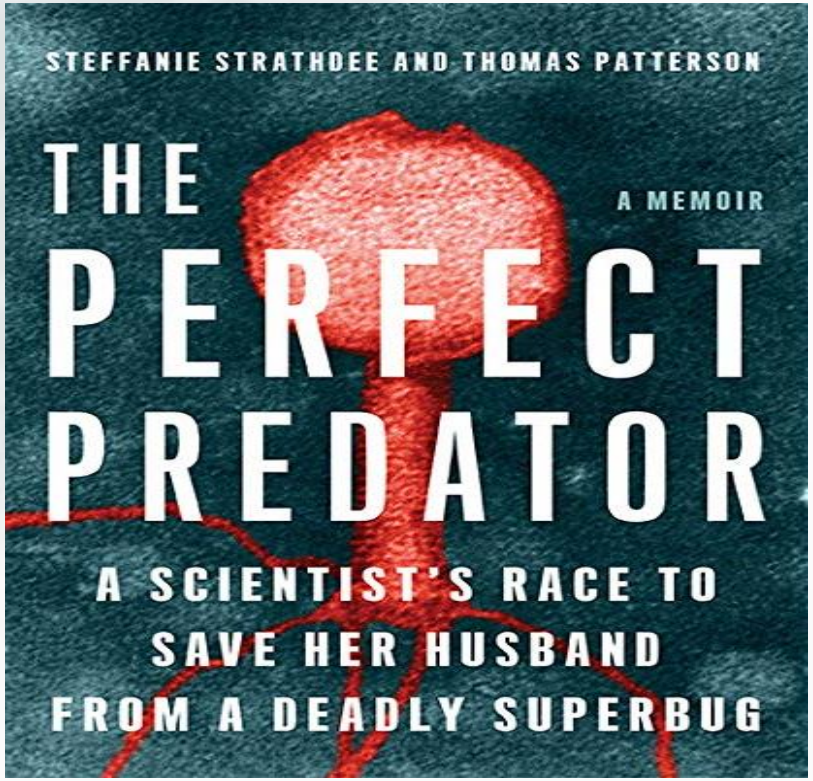
https://www.nbcsandiego.com/news/local/UCSD-Launches-Center-to-Combat-Superbugs-486324271.html

A current summary of human phage therapy trials and the range of target sites and infections



Dr. Steffanie Strathdee

Co-director of the Center for Innovative Phage Applications and Therapeutics



https://health.ucsd.edu/news/releases/Pages/2018-10-18-18-epidemiologist-strathdee-named-to-time-magazine-most-influential-in-health.aspx
http://sdcitybeat.com/special-issues/best-of-san-diego-people/people-of-the-year-2018-steffanie-strathdee/
https://ucsdnews.ucsd.edu/feature/times-list-of-50-most-influential-people-in-health-care-includes-a-real-phage-turner

Phage therapy Vs antibiotics

- High specificity
- Normal gut flora not affected
- An alternative for people that allergy to antibiotics
- Different modes of administration
- Single dose is often sufficient
- Safe and efficient
- Production is simple and inexpensive
- Can be use alone or conjugation with antibiotics

Problems

- Novelty
- Specificity of phages
- Efficacy and other technical challenges
- Regulatory approvals
- Patent protection
- Market acceptance

Phage therapy:
lack of regulatory framework make the final step
towards application too steep

Conclusion

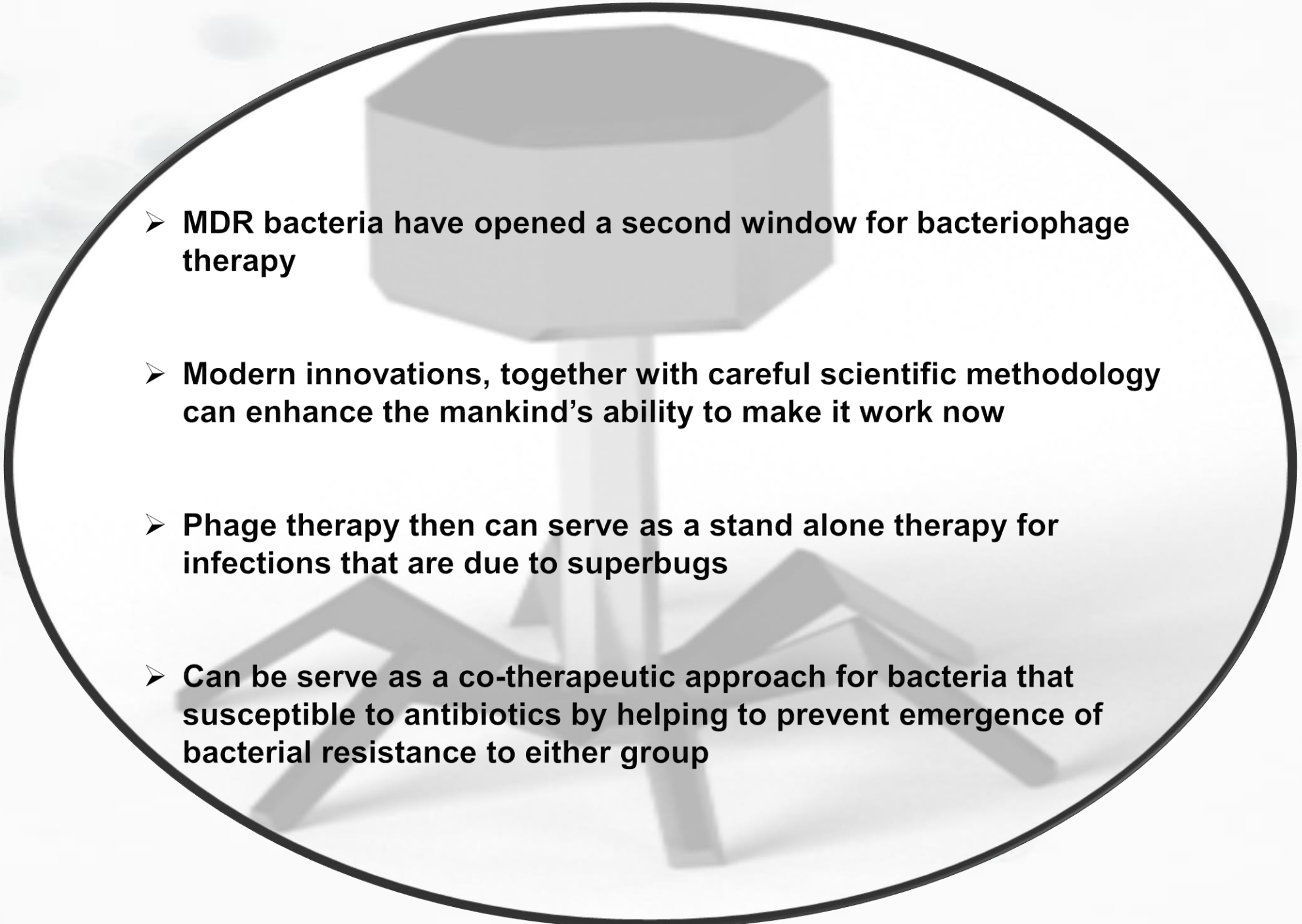
1. Phages are everywhere

2. Different strategies are possible:
   - lytic phages
   - lytic phage products
   - modified lysogenic phages for gene delivery
   - phages as probiotics?

3. Phages are safe

4. Phages are efficient, also against antibiotic resistant bacteria and against bacteria in biofilm

5. Clinical trials are held back because of 'safety' considerations and lack of appropriate regulatory framework



- MDR bacteria have opened a second window for bacteriophage therapy
- Modern innovations, together with careful scientific methodology can enhance the mankind's ability to make it work now
- Phage therapy then can serve as a stand alone therapy for infections that are due to superbugs
- Can be serve as a co-therapeutic approach for bacteria that susceptible to antibiotics by helping to prevent emergence of bacterial resistance to either group

Thank You