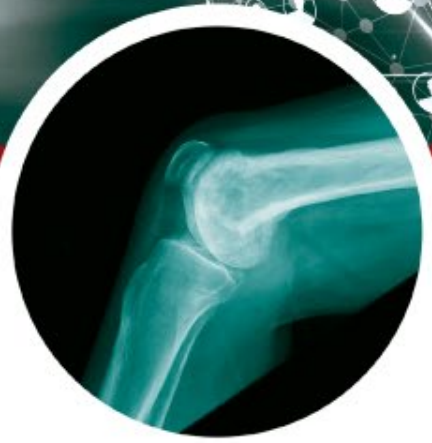
VIII Jornada grupo GEIO

GRUPO DE ESTUDIO DE INFECCIONES OSTEOARTICULARES

2023

NUEVOS RETOS EN INFECCIÓN OSTEOARTICULAR (IOA)

Utilidad y aplicación práctica de los fagos y las lisinas en la IOA



Madrid

GEIO · SEIMC

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Clínica Universidad de Navarra (Pamplona)

AGENDA

1. *¿Qué es un fago?*
2. *¿Dónde están los fagos?*
3. *Clasificación de los fagos*
4. *Morfología y estructura*
5. *Ciclo de un fago*
6. *Fagos versus antibióticos*
7. *Resistencia bacteriana a los fagos*
8. *Fagos y biofilms*
9. *Experiencia clínica en infección osteoarticular*
10. *Limitaciones al uso de la fagoterapia*
11. *El futuro*

2023

¿Qué tienen en común?

1. *Vibrio cholerae*
2. *Shigella dysenteriae*
3. *Corynebacterium diphtheriae*
4. *Clostridium botulinum*
5. *Staphylococcus aureus*
6. *Streptococcvus pyogenes*
7. *Salmonella entérica serovar Typhimurium*

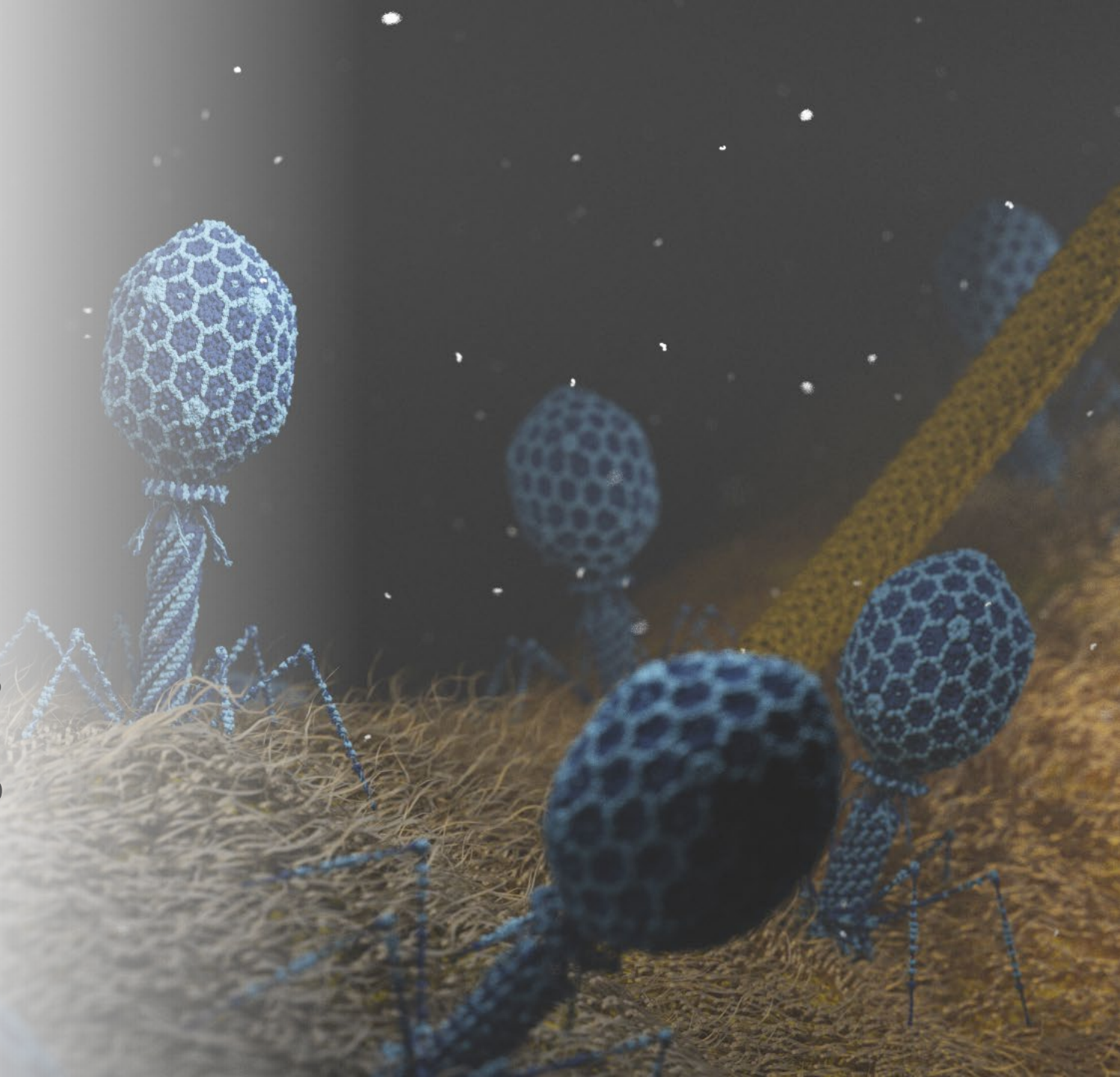
El 20% del genoma bacteriano proviene del genoma de fagos

¿Qué es un fago?

2023

Ahora mismo…..

- Hay unos 10^{31} fagos en la biosfera
- Se calcula que hay 10 millones de veces más fagos en los océanos que estrellas en el universo.
- Están ocurriendo más de 10^{25} infecciones por fagos por segundo
- Se están produciendo más de 10^{15} transferencias de genes procedentes de fagos por segundo



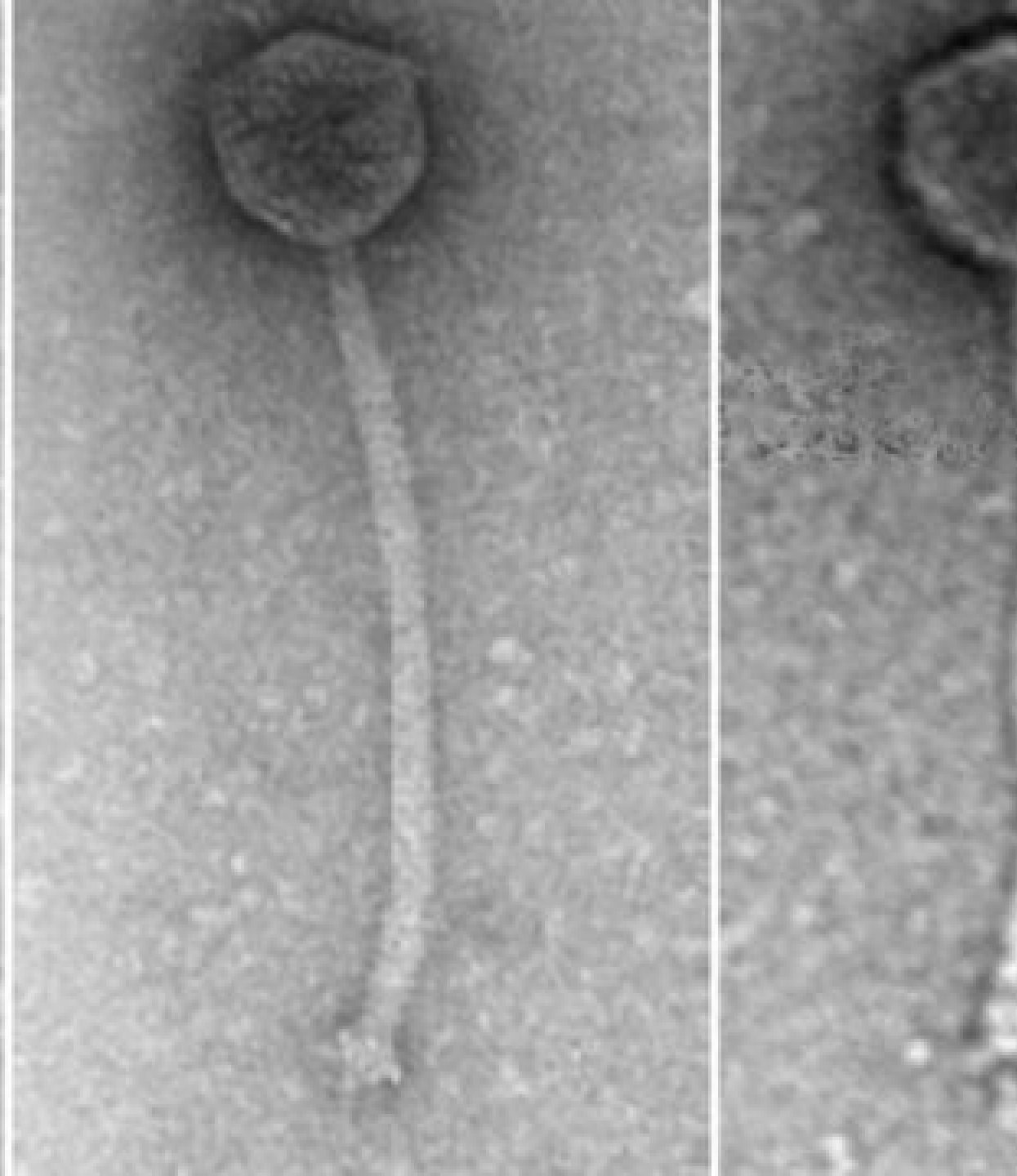
Phage Therapy: Past, Present and Future

Madeline Barron ASM 2022

- Bacteriófagos: virus que infectan bacterias (Fagoterapia)
- Primeros estudios (1915) prometedores, aunque mal diseñados (no grupos control).
- Resultados en revistas inaccesibles.
- A lo largo de la década de 1940, varias empresas farmacéuticas de US produjeron preparados de fagos para tratar diversas infecciones (piel, tracto respiratorio,…)

Después comenzó la ERA ANTIBIÓTICA…

Y luego vino la era POST-ANTIBIÓTICA…



¿Dónde están los fagos?

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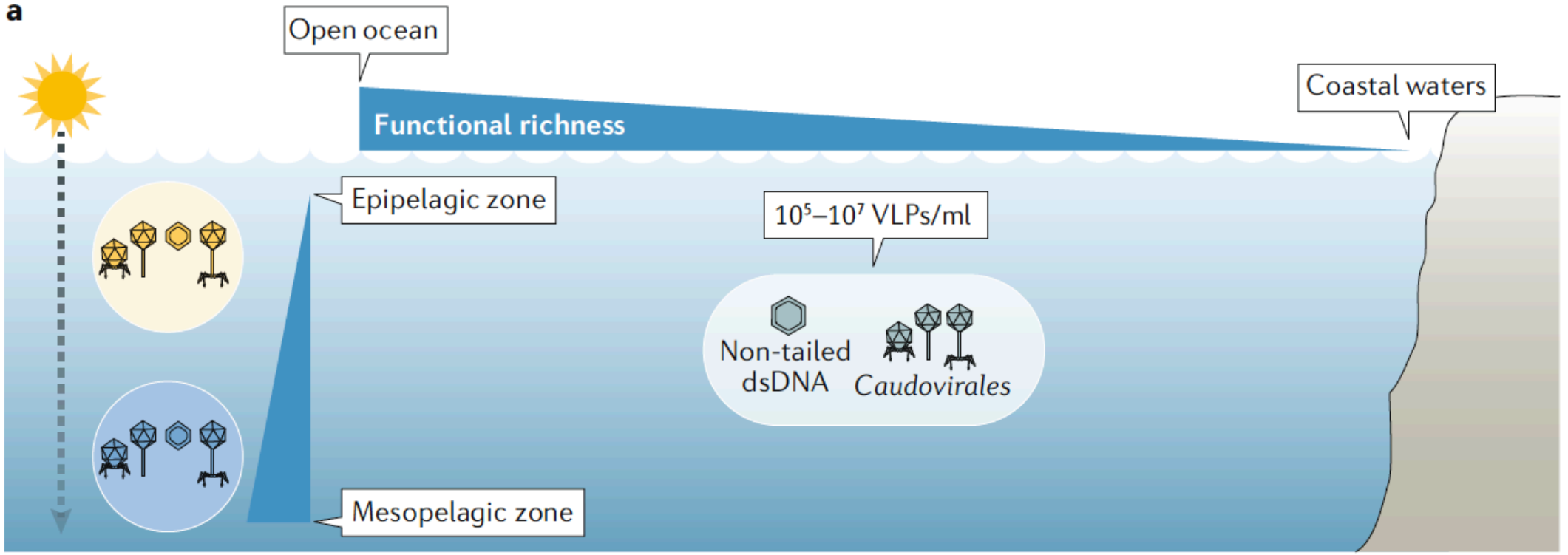
Phage diversity, genomics and phylogeny

Moïra B. Dion et al., Nature Revs Microbiol 2020

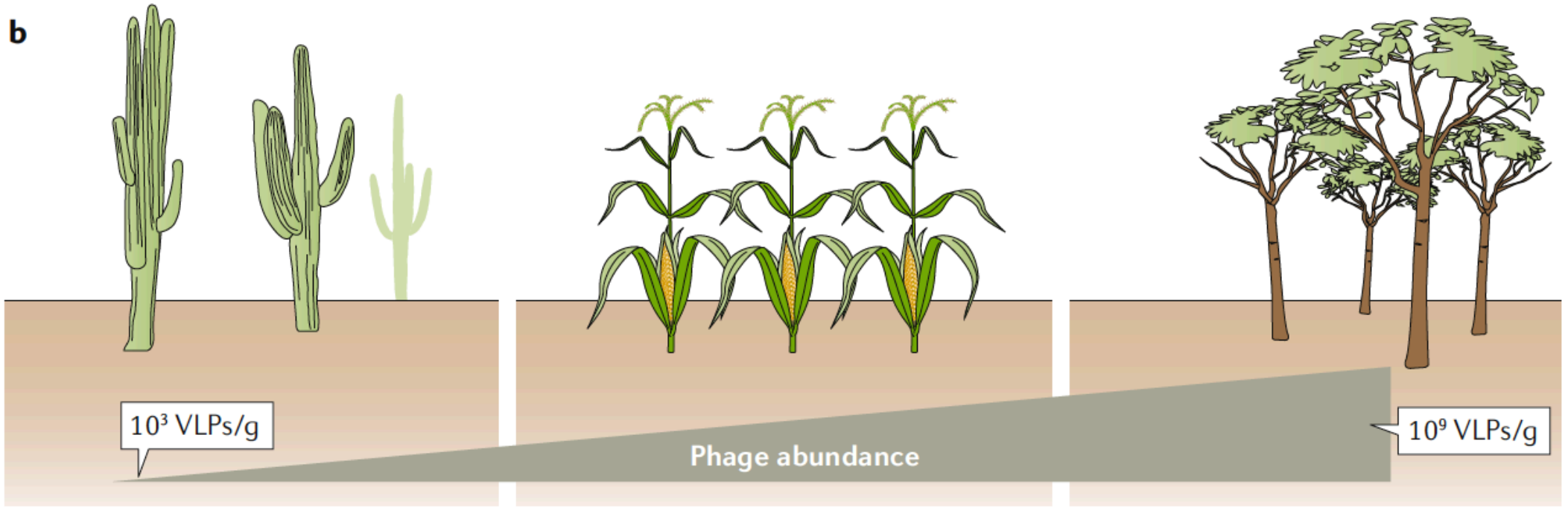
Phages in the marine environment are extremely abundant, with a virus- to-bacteria ratio often ranging from 1:1 to 100:1



Phage diversity, genomics and phylogeny

Moïra B. Dion et al., Nature Revs Microbiol 2020

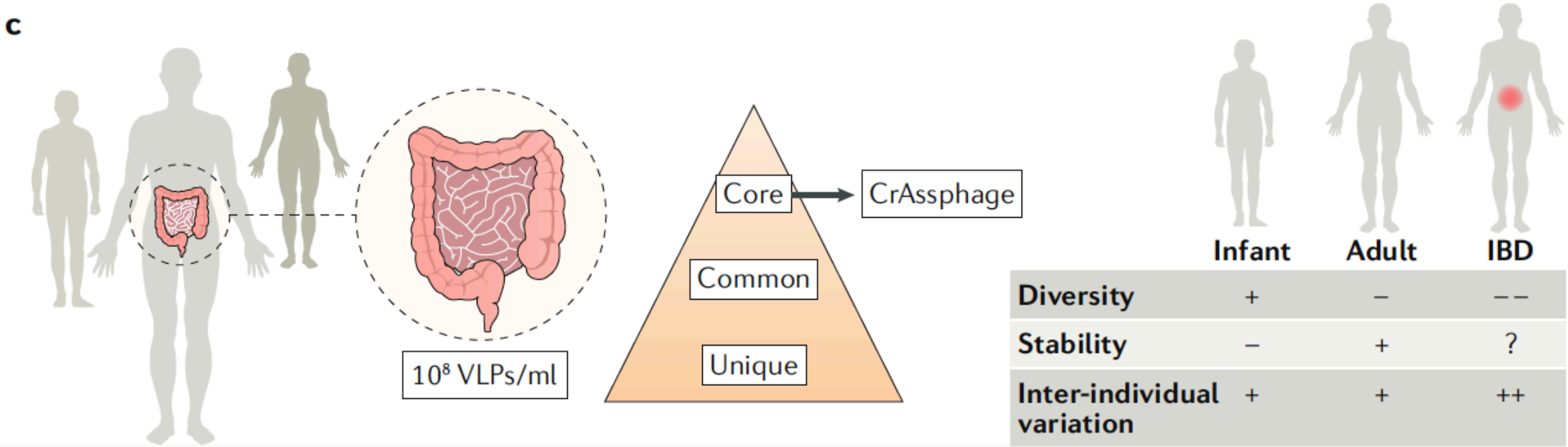
Phage abundance in the soil is highly variable and correlates with biome type (for example, desert, agricultural or forest soils), pH and bacterial abundance



Phage diversity, genomics and phylogeny

Moïra B. Dion et al., Nature Revs Microbiol 2020

Changes in the diversity and composition of the human virome were also reported to be related to the gut health status, particularly in the case of inflammatory bowel disease

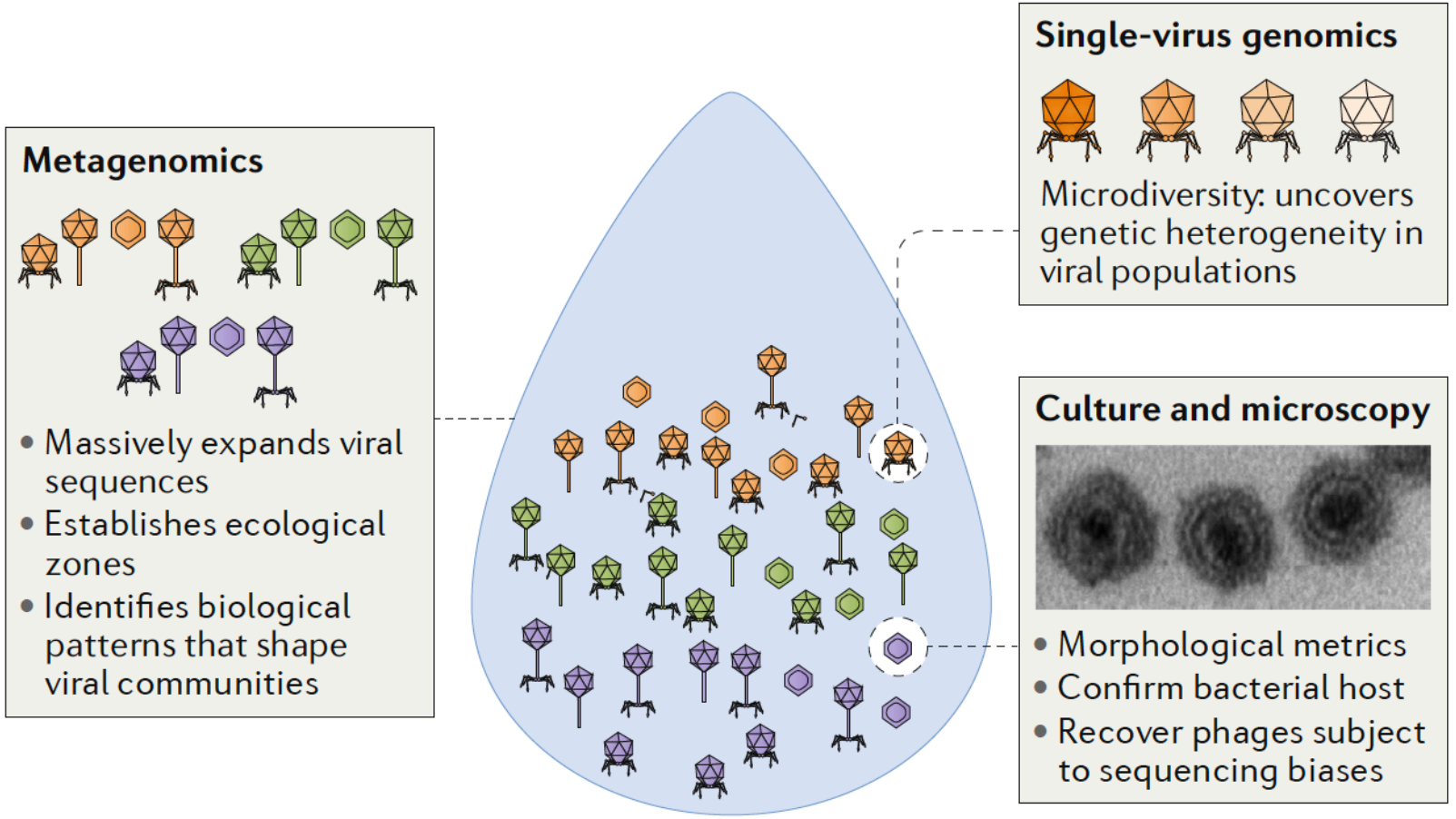


	Infant	Adult	IBD
Diversity	+	–	– –
Stability	–	+	?
Inter-individual variation	+	+	++

Phage diversity, genomics and phylogeny

Moïra B. Dion et al., Nature Revs Microbiol 2020

Phage composition is unique to individuals (FAGOMA), with global metagenomic analyses indicating that some phages are globally distributed



Clasificación de los fagos

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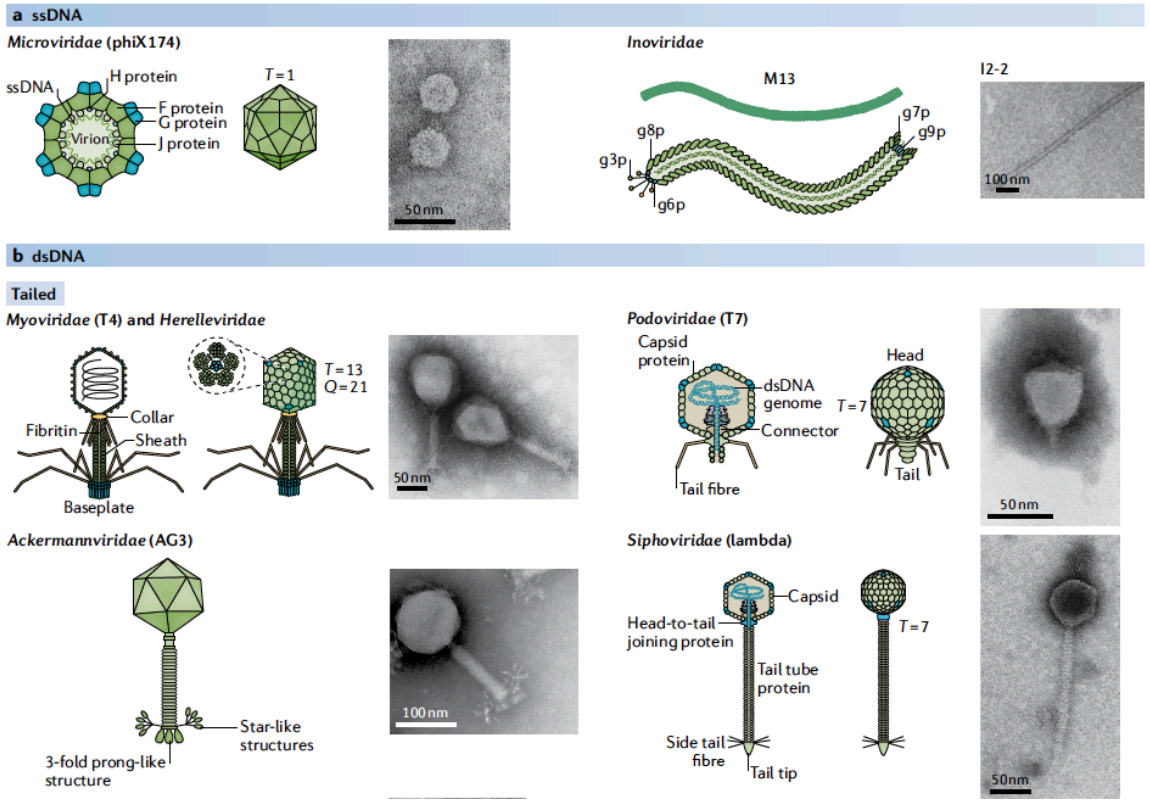
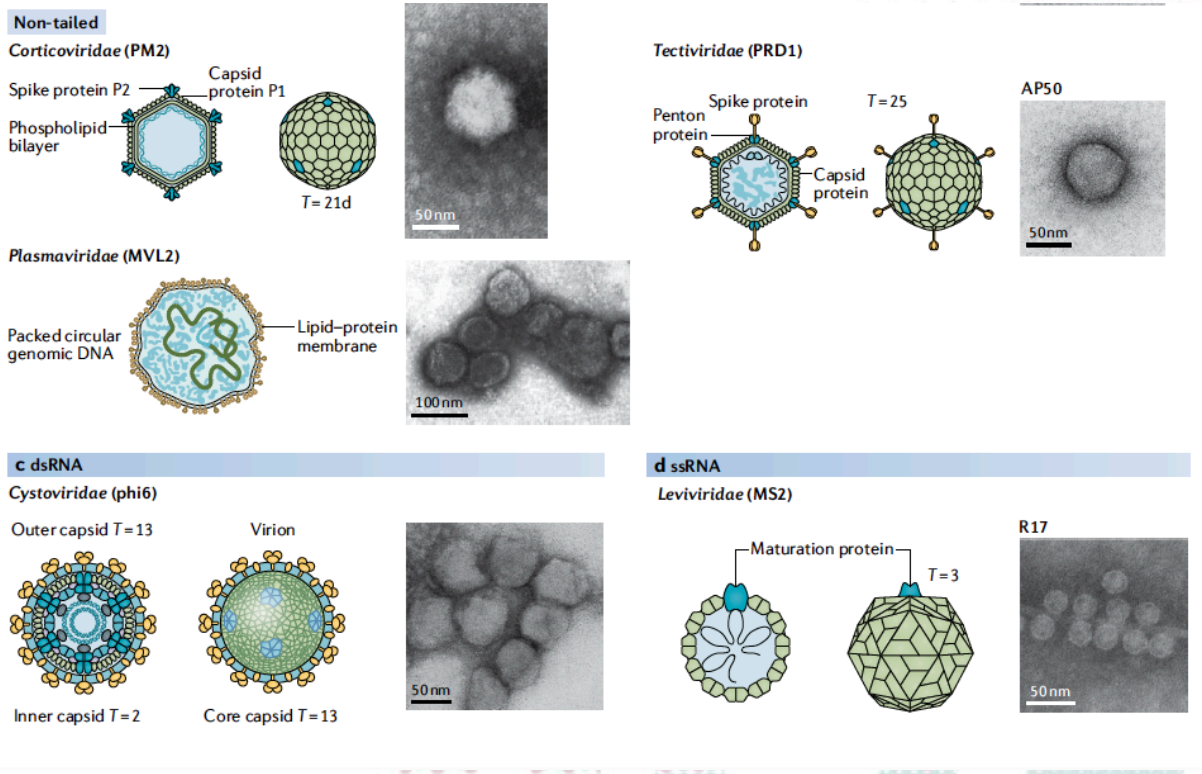
Phage diversity, genomics and phylogeny

Moïra B. Dion et al., Nature Revs Microbiol 2020

Phage classification based on morphology and genome type





Phage diversity, genomics and phylogeny

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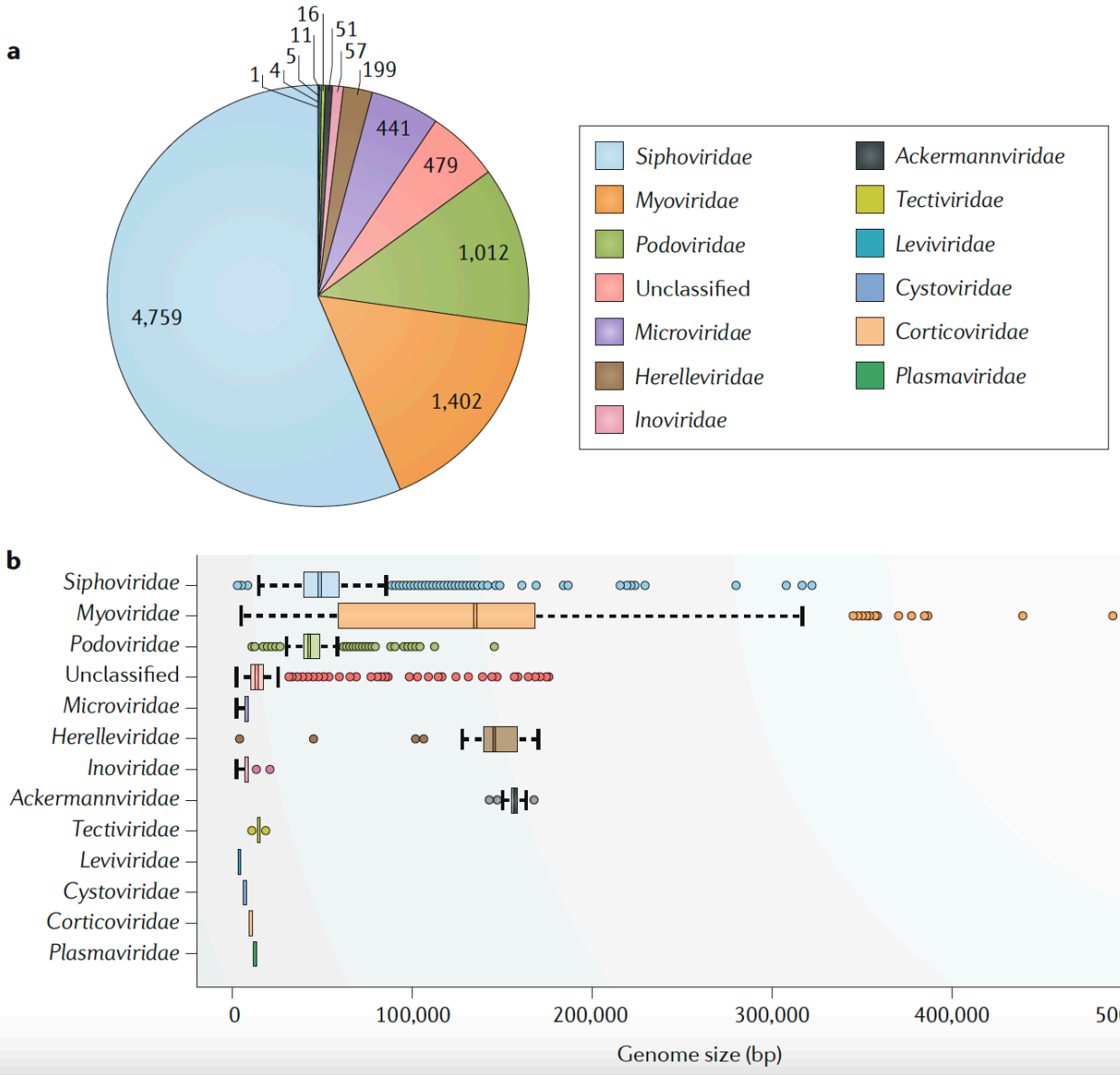
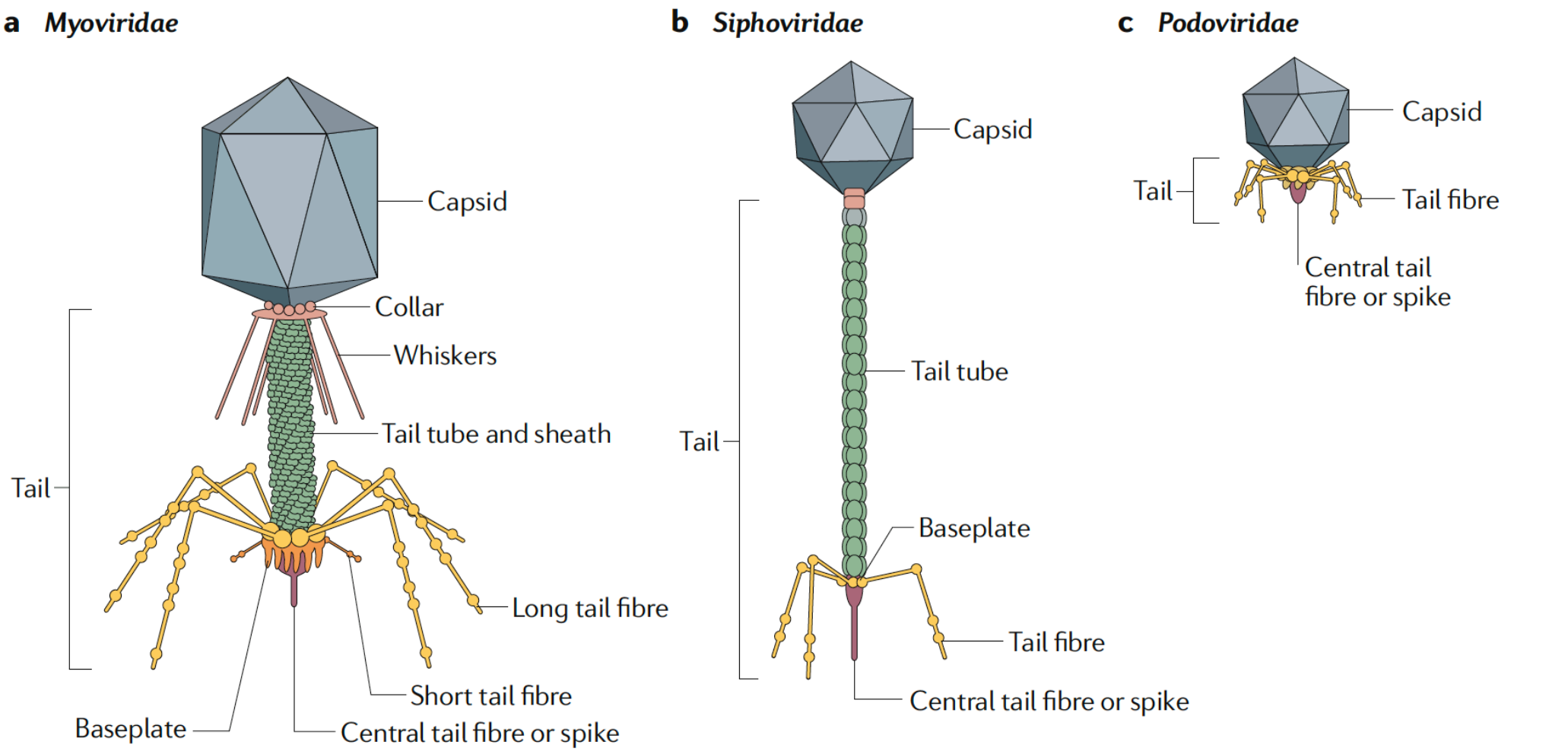


Morfología y estructura

2023

Targeting mechanisms of tailed bacteriophages

Franklin L. Nobrega et al., Nature Revs Microbiol 2020



Phage Therapy: A Renewed Approach to Combat Antibiotic-Resistant Bacteria

Kaitlyn E. Kortright et al., Cell Host & Microbe 2019

- Phage encode binding proteins that recognize and attach to sites on the surface of a bacterial cell. Many phage bind to protein structures on the bacteria such as **pili** (red), **flagella** (yellow), **porins** (blue), or **efflux pumps** (purple). Phage have also been reported to bind to specific sugar moieties in **LPS** (green).

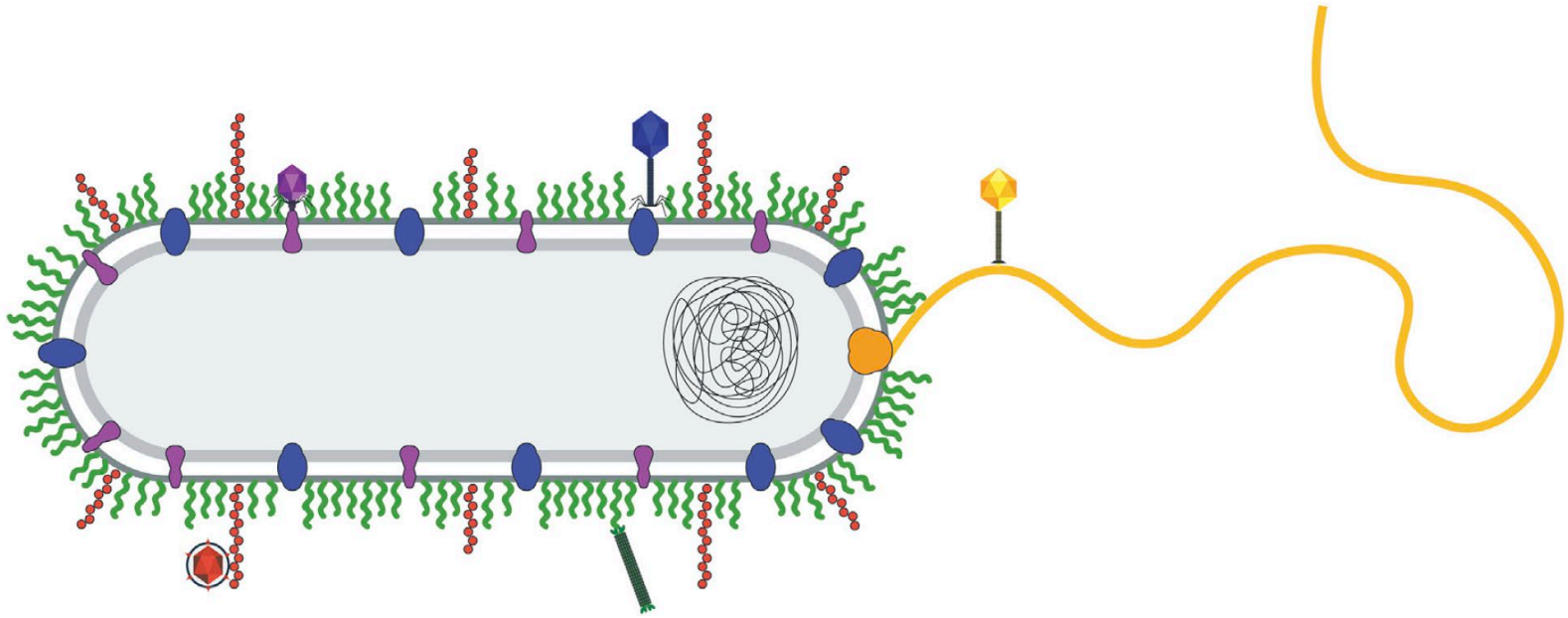
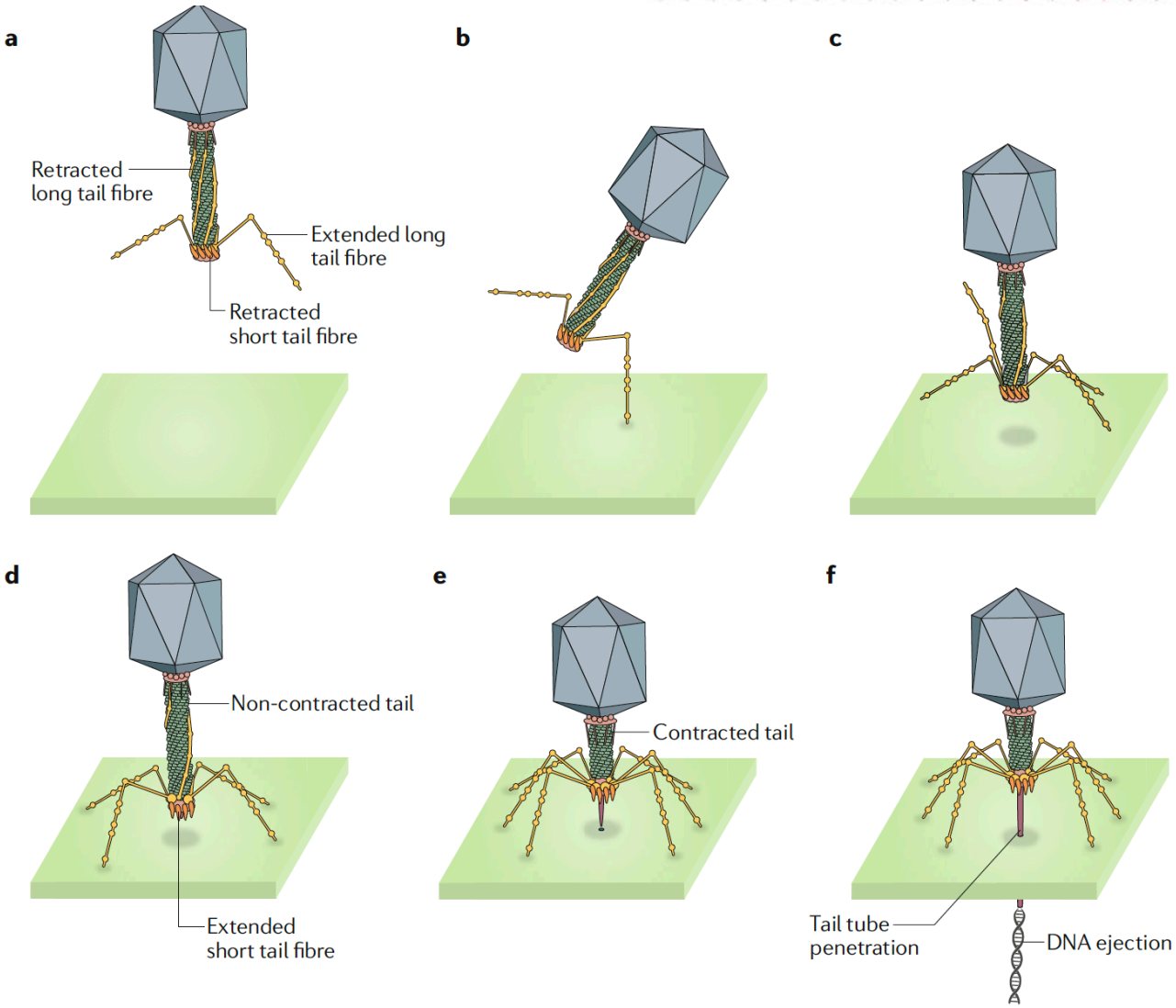


Figure 2. Examples of Bacterial Receptors for Phage Binding

Phage encode binding proteins that recognize and attach to sites on the surface of a bacterial cell. Many phage bind to protein structures on the bacteria such as pili (red; e.g., Mindich et al., 1976), flagella (yellow; e.g., Choi et al., 2013), porins (blue; e.g., Furukawa and Mizushima, 1982), or efflux pumps (purple; e.g., Chan et al., 2016). Phage have also been reported to bind to specific sugar moieties in LPS (green; e.g., Mindich et al., 1976).

Targeting mechanisms of tailed bacteriophages

Franklin L. Nobrega et al., Nature Revs Microbiol 2020



Ciclo de un fago

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Phage Therapy: A Renewed Approach to Combat Antibiotic-Resistant Bacteria

Kaitlyn E. Kortright et al., Cell Host & Microbe 2019

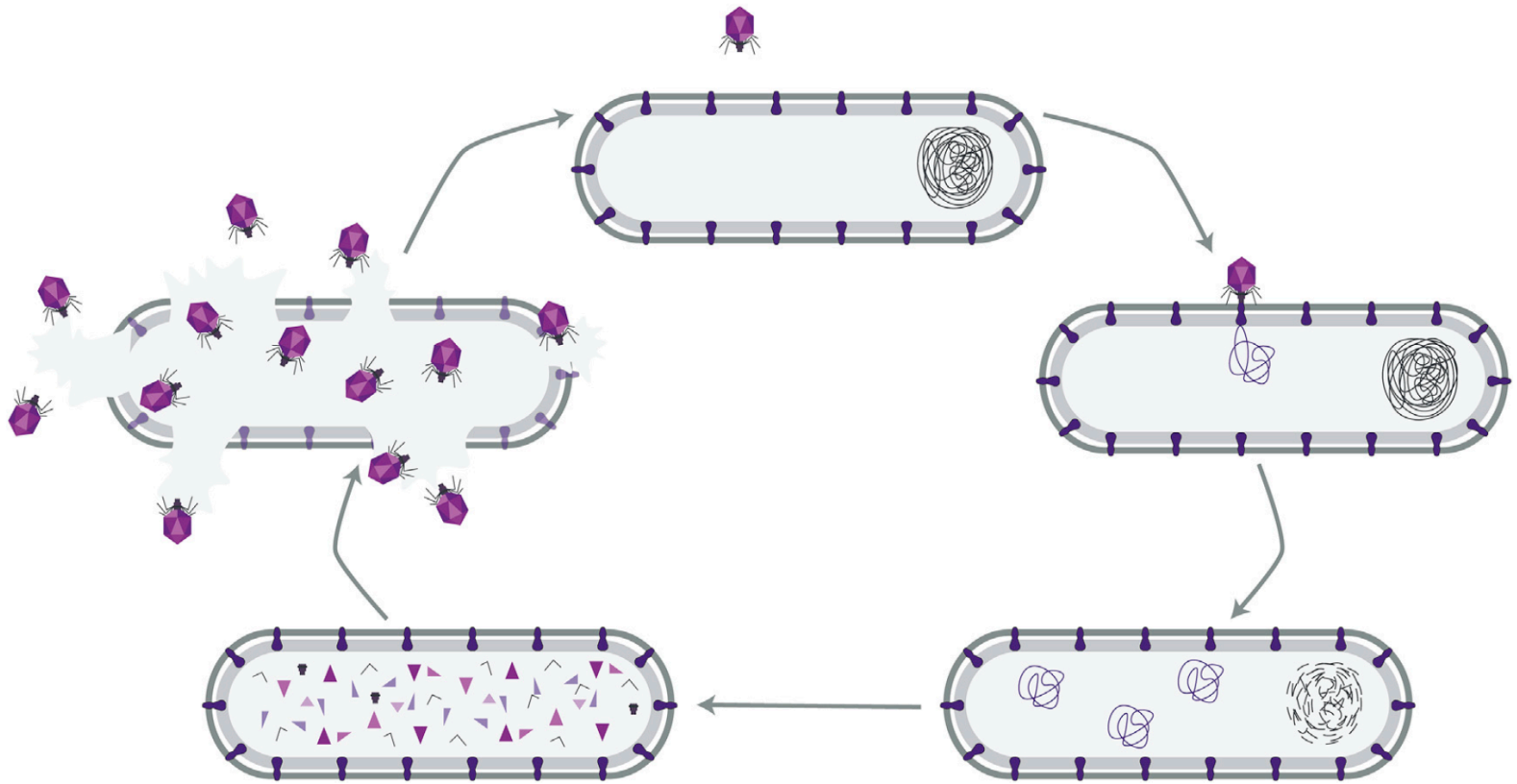


Figure 1. Lytic Phage Infection Cycle

A cycle of lytic phage replication begins when the virus recognizes and irreversibly binds to a receptor (protein or sugar) on the surface of a bacterial cell. The phage delivers its genomic content into the cytoplasm of the bacterial cell. Typically, host resources, including proteins and genomes, are repurposed to fuel phage replication. Replication, transcription, and translation of the phage genome begins usually through redirecting host metabolism to the production of new phage particles. Upon assembly of new phage particles, lysis of the bacterial cell allows newly replicated phage particles to escape the cytoplasm and go on to infect other susceptible bacteria.

Implications of Bacteriophage- and Bacteriophage Component-Based Therapies for the Clinical Microbiology Laboratory

Katherine M. Caflischa and Robin Patel JCM 2019

Lysogenic, phages don't kill their bacterial prey outright—they integrate their genome into the host cell.

Vehicles and environmental reservoirs for:

- Antimicrobial resistance genes
- Toxin genes
- Has net effects on bacterial fitness and relevance to the evolution

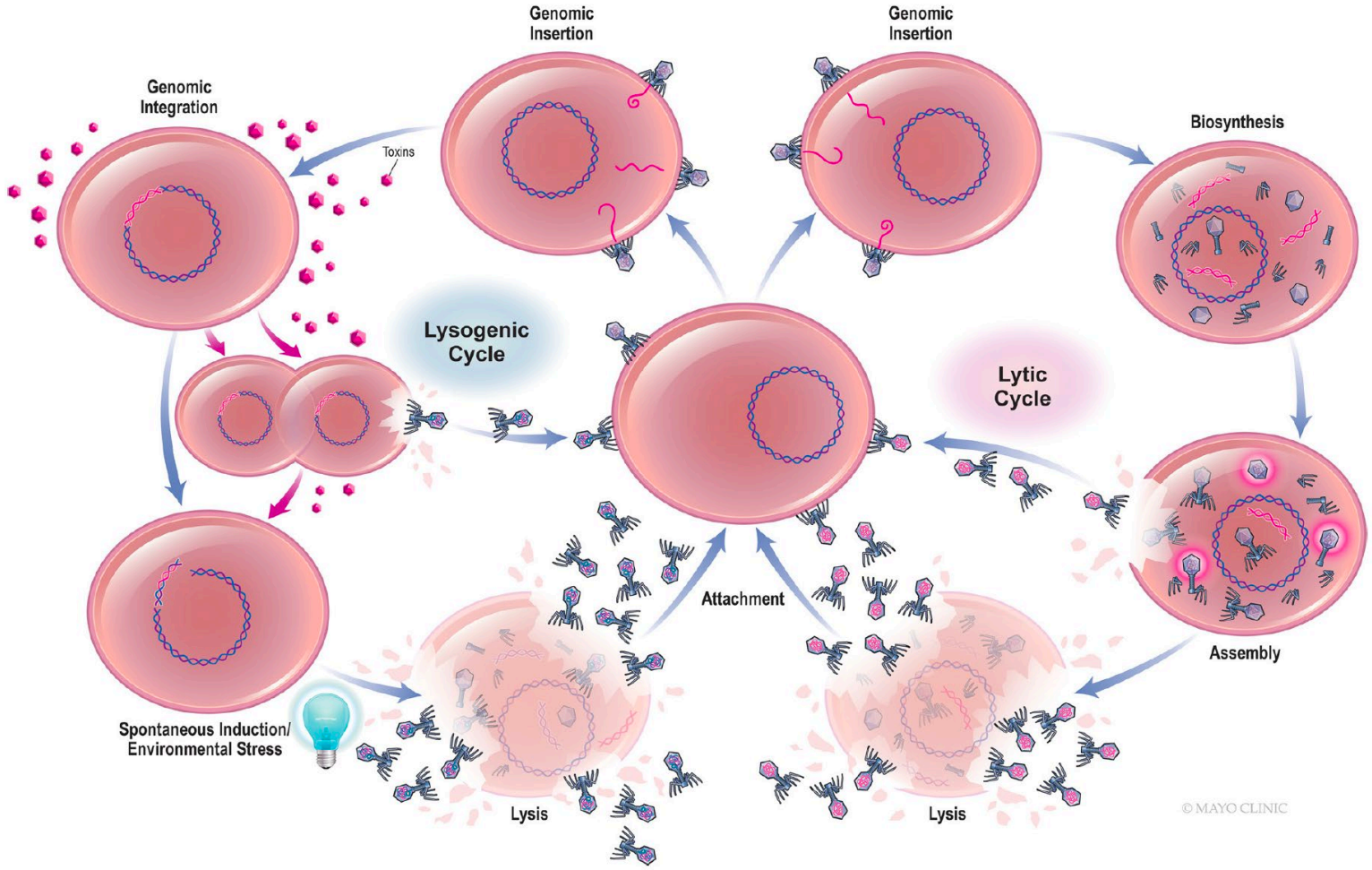


FIG 1 Bacteriophage life cycle.

The Age of Phage: Friend or Foe in the New Dawn of Therapeutic and Biocontrol Applications?

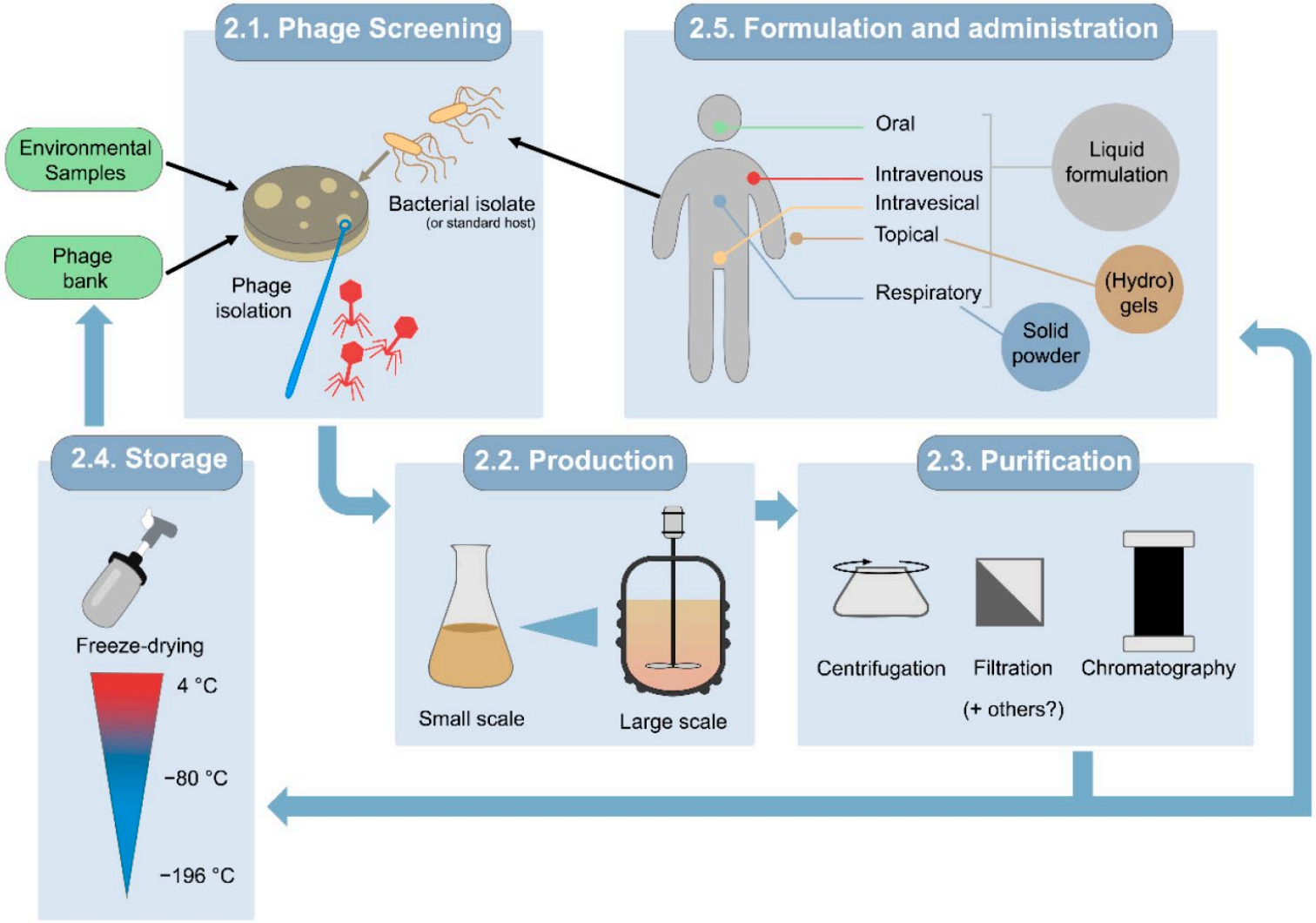
Hassan, A.Y.; et al., Pharmaceuticals 2021

Table 1. Observed phage-mediated transduction events involving antibiotic resistance genes among bacterial pathogens identified as part of the World Health Organization's Priority Pathogens since 2010.

Bacterial Pathogen	Phage	Resistance Gene	Antibiotic	Reference
Acinetobacter baumannii	Unknown	*armA* bla_{TEM-1} *tet*(B) *gyrA*-81L	Aminoglycoside resistance B-Lactamase resistance Tetracycline resistance Nalidixic Acid resistance	[122]
Acinetobacter baumannii	Unknown	bla_{NDM-1}	B-Lactamase resistance	[135]
Pseudomonas aeruginosa	Unknown	bla_{VIM} bla_{TEM} *mecA* *qnrA* *qnrS*	B-Lactamase resistance Methicillin resistance Quinolone resistance	[136]
Staphylococcus aureus	Φ19	*erm*(C)	Erythromycin resistance	[137]
Staphylococcus aureus	Φ20	*erm*(C)	Erythromycin resistance	[137]
Staphylococcus aureus	80α	*erm*(C)	Erythromycin resistance	[137]
Staphylococcus aureus	Φ52A	tetK cadD blaZ	B-Lactamase resistance	[127]
Staphylococcus aureus	Φ80α	*tet*K *cad*D *bla*Z	Tetracycline resistance	[127]
Staphylococcus aureus	Φ29	*tet*K	Tetracycline resistance	[127]
Escherichia coli	933W	*tet*(A)	Tetracycline resistance	[132]
Escherichia coli	Various	bla_{TEM} *floR* *aphA1* *tet*(A)	Ampicillin resistance Chloramphenicol resistance Kanamycin resist Tetrac	
Escherichia coli	Unknown	*qnr*A *qnr*S		
Escherichia coli	Unknown			

Essential Topics for the Regulatory Consideration of Phages as Clinically Valuable Therapeutic Agents: A Perspective from Spain

Roberto Vázquez et al., Microorganisms 2022



Implications of Bacteriophage- and Bacteriophage Component-Based Therapies for the Clinical Microbiology Laboratory

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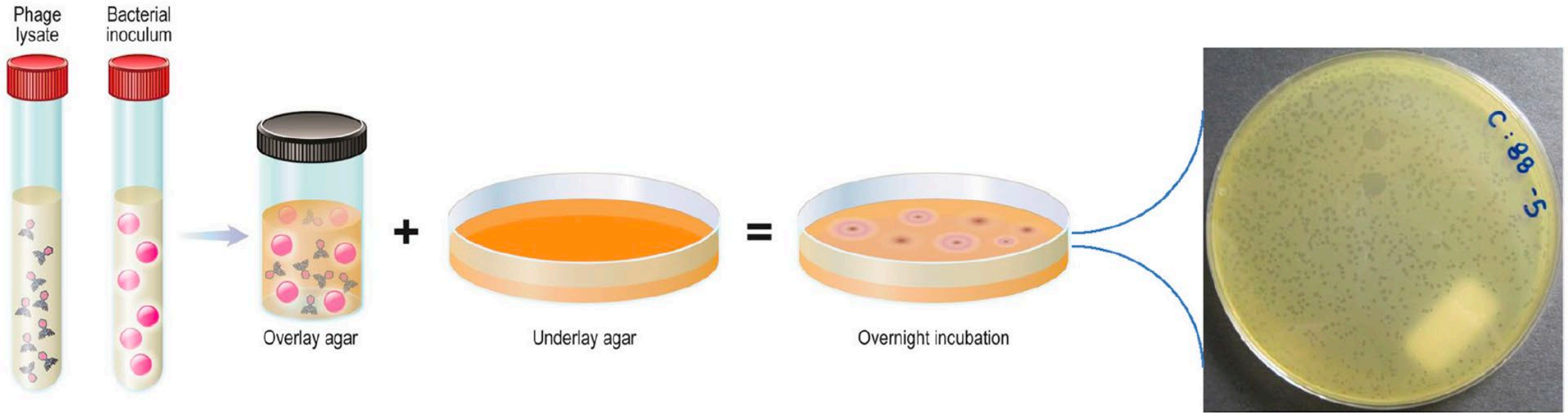

FIG 2 Double-overlay plaque assay. A combination of amplified phage and host bacterium in cooled, molten agar supplemented with divalent cations (e.g., $CaCl_2$, $MgSO_4$) is poured over solid agar and the medium is incubated overnight. Quantifiable clearings (plaques) in the bacterial lawn indicate the presence of infectious phage. At least two different plaque morphologies are observed in the example photograph, illustrating an experiment involving coculture of *Salmonella enterica* serotype Typhimurium and phages obtained from municipal sewage. (© Mayo Clinic).

Fagos y antibióticos

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Phage therapy in the Covid-19 era: Advantages over antibiotics

Atif Khan et al., Current Research in Microbial Sciences 2022

Criteria	Antibiotics	Bacteriophages
Specificity to bacteria	Non-specific, Non-target organisms, including normal flora of the body, gets killed.	Highly specific for its bacterial host and does not disturb beneficial bacteria.
Resistance	Broad-spectrum antibiotics are repeatedly used to treat various infections and therefore, more chances of resistance development.	Phage specificity limits the use of specific phage and therefore, limited chances of resistance development
Mode of action	Inhibitory action over DNA, RNA, Protein, or cell wall synthesis	Cell lysis
Effectivity on bacterial biofilms	Less effective due to penetration barrier and biofilm-associated antibiotics resistance	Most phages have EPS degrading enzymes like depolymerase, which help them to penetrate and kill the host
Dose	Systemic dose (i.e., equally distributed in the entire body).	The higher number near the site of infection (targeted therapy)
Effect on the immune system	Direct effect by many immunomodulatory antibiotics and indirect effect via dysbiosis	Highly purified phage preparations have a negligible immune response. Few phages act as an immunomodulator
Environmental impact	An environmental release may lead to waterbody contamination and the development of antibiotic resistance	The shorter life (outside host) and non-availability of a host lead to rapid elimination from the environment.

The Age of Phage: Friend or Foe in the New Dawn of Therapeutic and Biocontrol Applications?

Hassan, A.Y.; et al., Pharmaceuticals 2021

Phage still have some **limitations** compared to traditional chemical antibiotics that need to be addressed before phage therapy can be fully accepted in modern clinical practice:

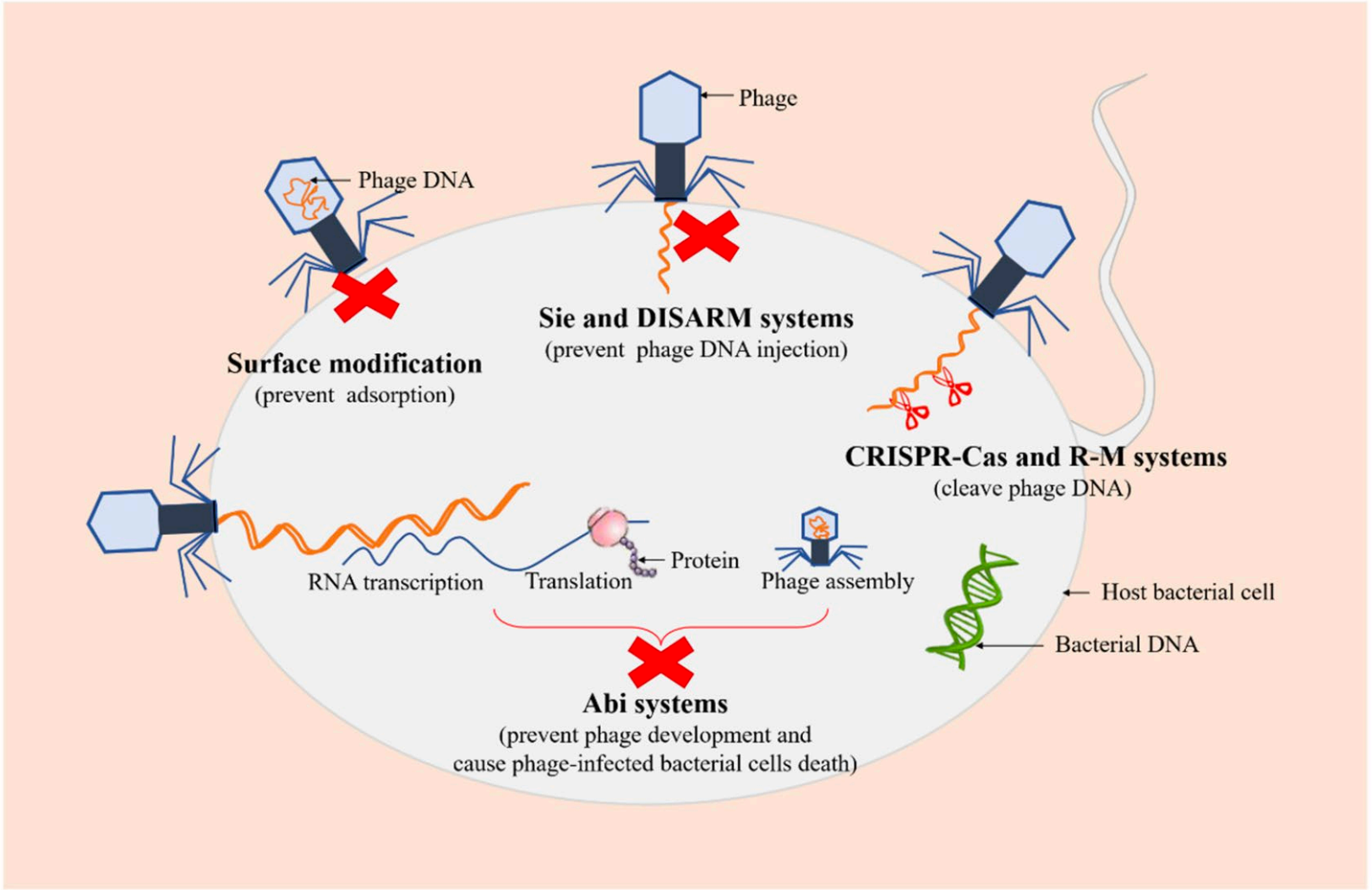
1. Phage are not an appropriate therapeutic for all infections (**intracellular bacteria**)
2. Interactions with the **immune system** has yet to be ellucidated
3. **Neutralizing antibodies** against certain phage typically associated with humans may be a general obstacle for phage therapy.
4. Widespread lysis of target bacteria can potentially release bacterial antigens that could be dangerous. **Generation of endotoxins** during therapy.
5. **Regulatory hurdles** represent a significant barrier to the implementation of phage therapy in modern medicine

Resistencia bacteriana a los fagos

2023

Phages against Pathogenic Bacterial Biofilms and Biofilm-Based Infections: A Review

Siyu Liu et al., Pharmaceutics 2022



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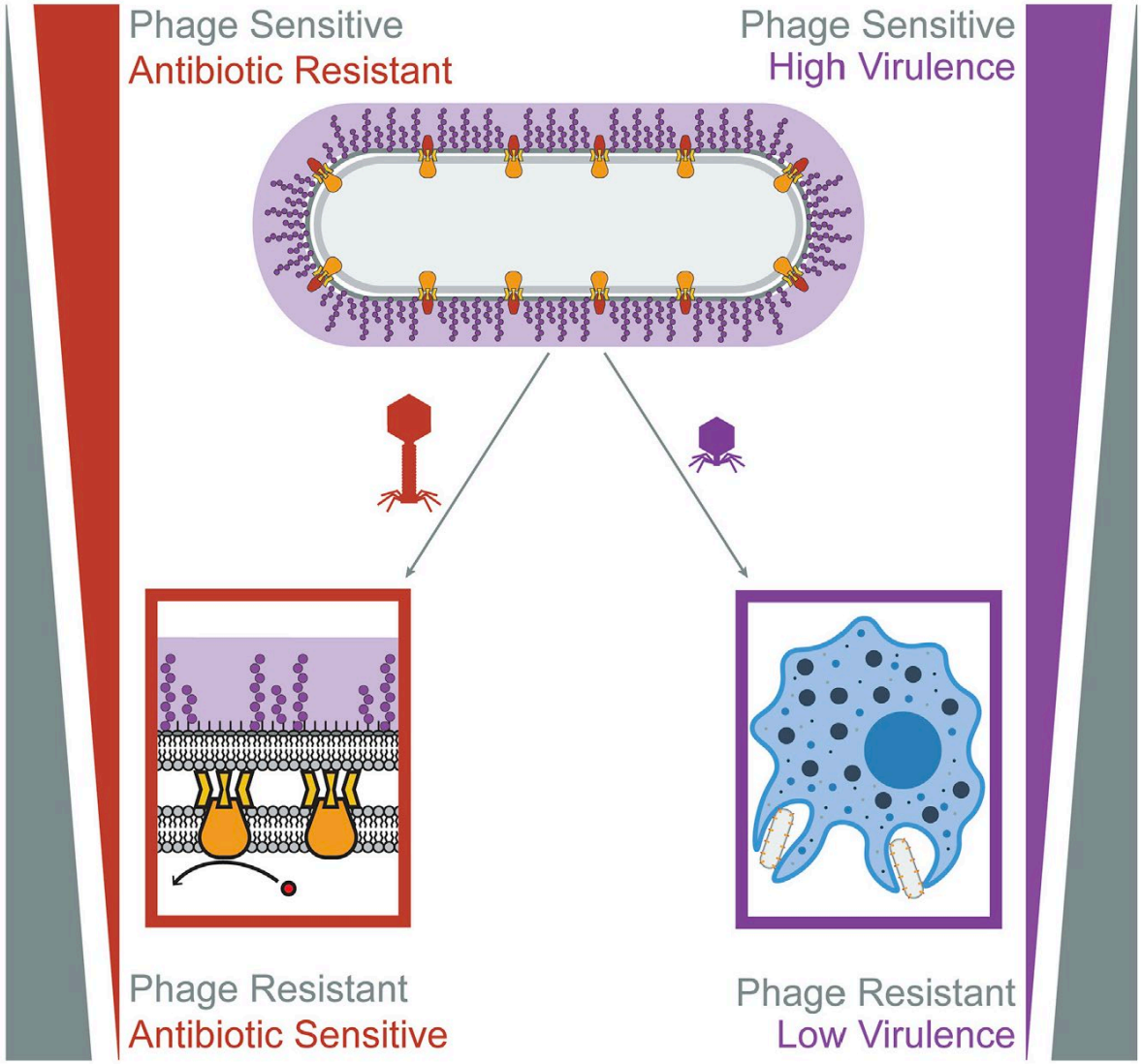
Kaitlyn E. Kortright et al., Cell Host & Microbe 2019



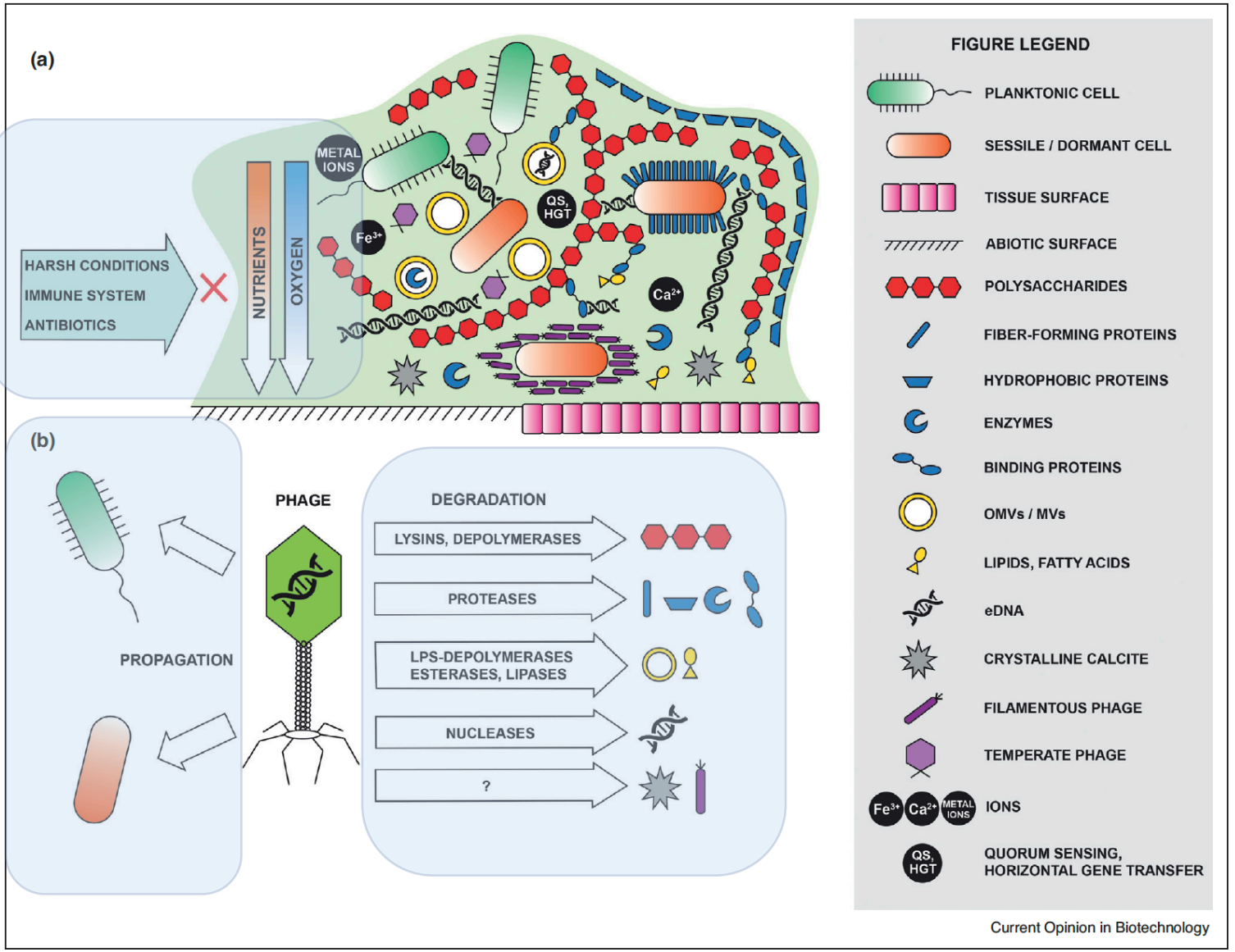
Phage that attach to an antibiotic efflux pump to infect may select against the expression of the efflux pump, rendering the bacteria more sensitive to antibiotics that were previously effluxed

Fagos y Biofilm

2023

Targeting biofilms using phages and their enzymes

Joana Azeredo et al., Current Opinion in Biotechnology 2021,



Bacteriophage-Mediated Control of Biofilm: A Promising New Dawn for the Future

Cheng Chang et al., Frontiers in Microbiol 2022

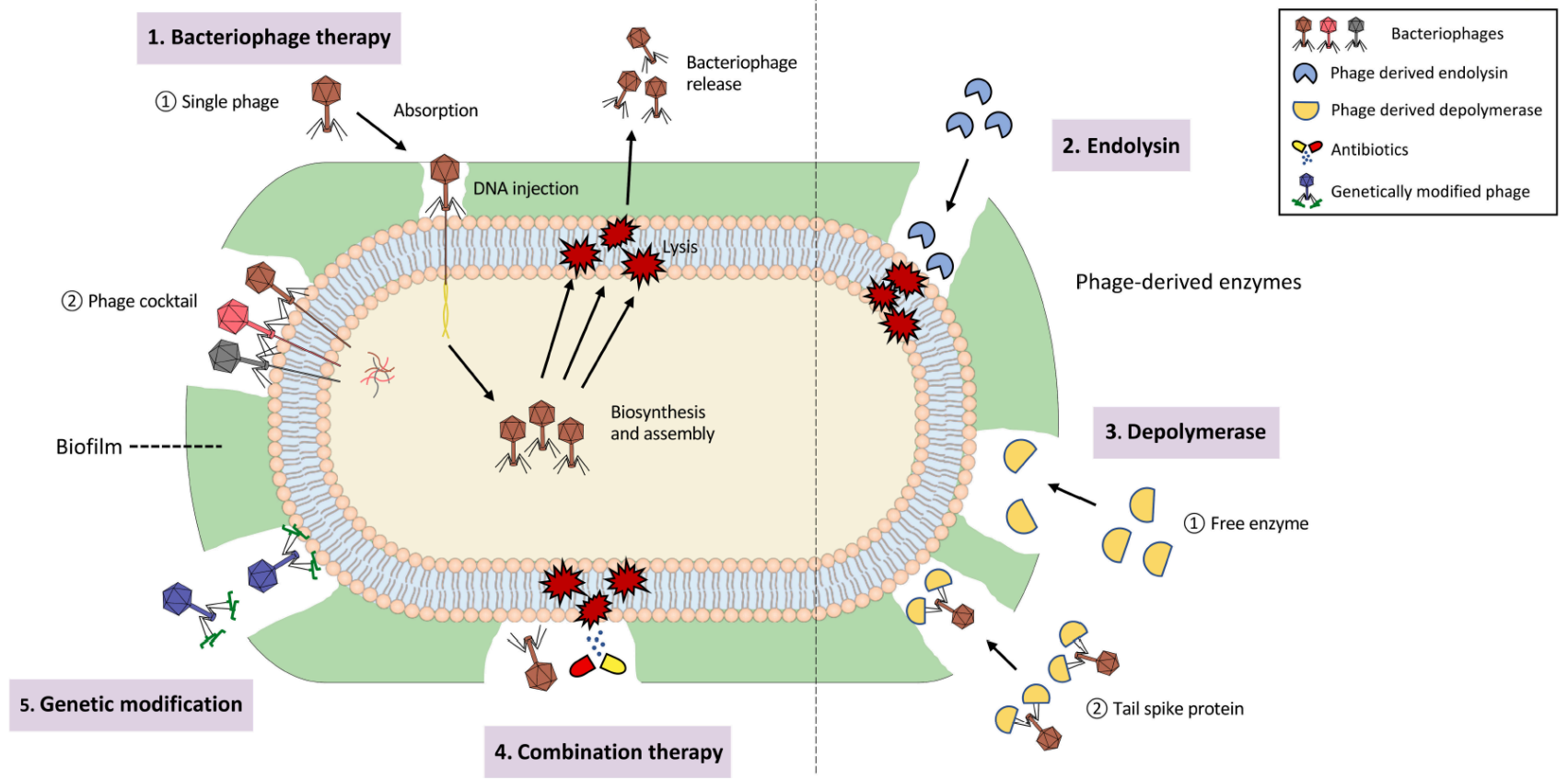


FIGURE 3 | Depiction of biofilm removal using phages and its derived enzymes. (1). Bacteriophage therapy, consisting of single phage therapy and cocktail therapy, that is used for intra- to extracellular degradation of the bacterial structure. (2). Phage-derived endolysin used for extra- to intracellular degradation of the bacterial structure. (3). Phage-derived depolymerase, presented as free enzyme or tail spike protein, that is used for chemical dispersion of the biofilm matrix. (4). Combination therapy using both phages and other antimicrobial compounds, such as antibiotics. (5). Genetically-modified phages that enlarge the host-species interaction range.

Could phages mean the end of device-related infections?

Del Pozo et al., Int J Artif Organs 2007

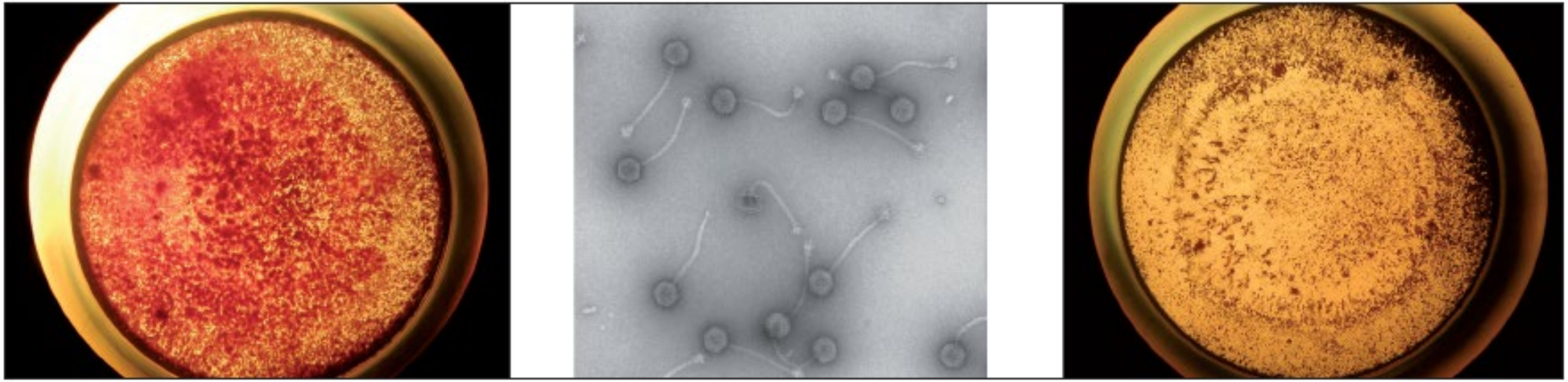
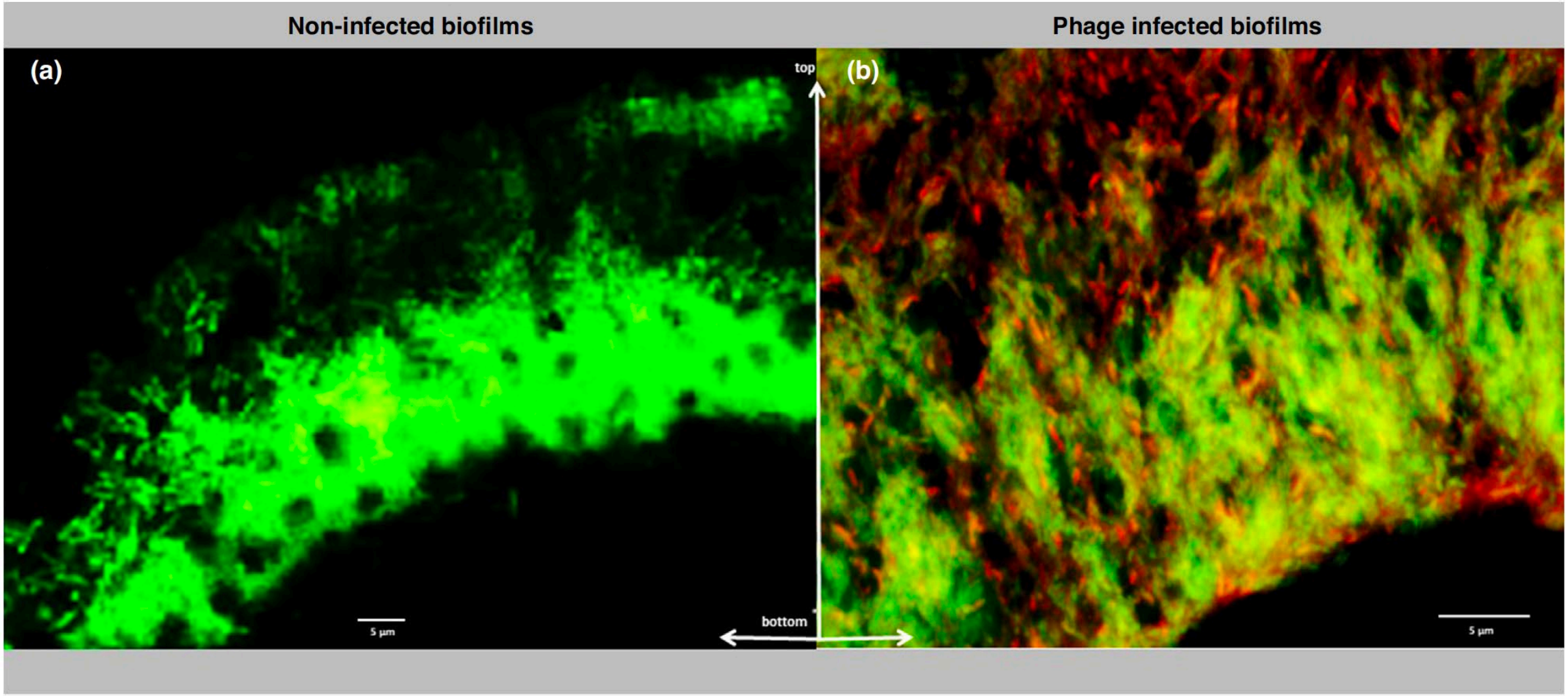


Fig. 3 - *Lysis to kill. Figures show phage λ80 wiping out a* Staphyloccus aureus *biofilm:* ***a)*** *24-hour biofilm before phage treatment;* ***b)*** *transmission electron microscopy of phage λ80;* ***c)*** *the same biofilm after 24 hours of phage contact.*

Targeting biofilms using phages and their enzymes

Azeredo et al. et al., Current Opinion in Biotechnology 2021



Current Opinion in Biotechnology

Bacteriophage-Mediated Control of Biofilm: A Promising New Dawn for the Future

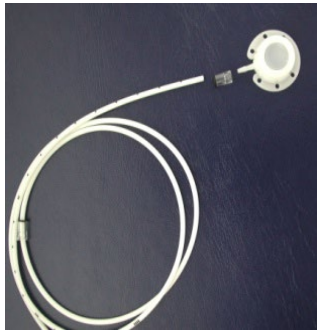
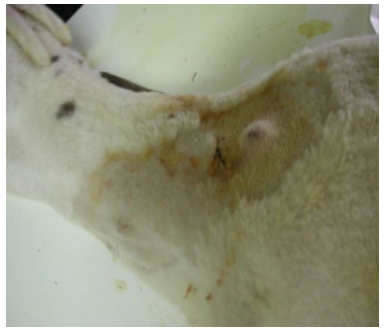
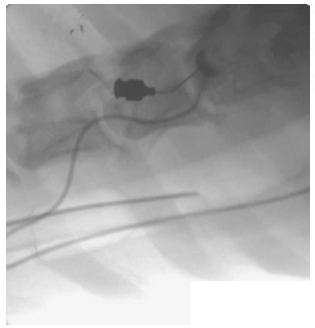
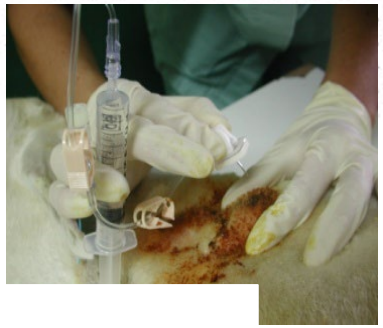
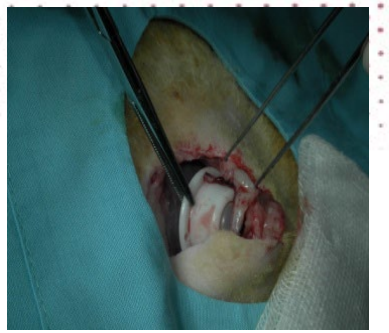
Cheng Chang et al., Frontiers in Microbiol 2022

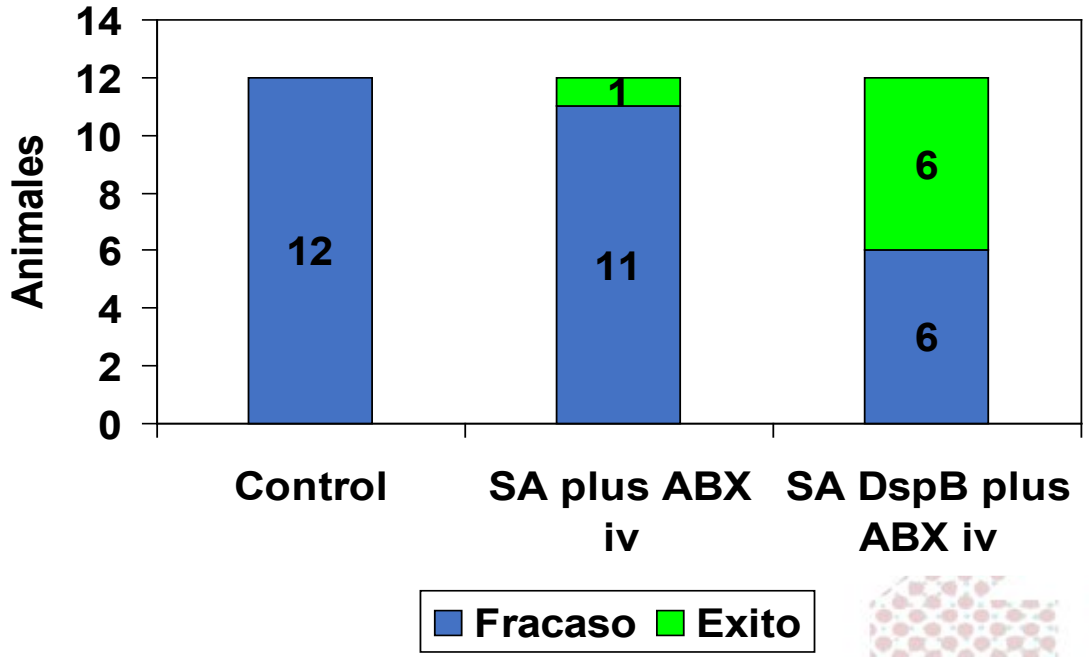
TABLE 2 | Anti-biofilm lysin studies.

Author, year	Biofilm-forming bacteria	Phage strain(s)/lysin	Growth site	Results
Landlinger et al., 2021	*Gardnerella*	PM-477 (engineered lysin)	vaginal swabs from BV (bacterial vaginosis) patients	For the majority of the samples, PM-477 demonstrated disruption of biofilm without affecting the remaining vaginal microbiome
Sosa et al., 2020	*S. aureus*	PlySs2	Murine tibial implant	PlySs2 and vancomycin used together *in vivo* reduced the number of CFUs on the surface of implants by 92%
Fursov et al., 2020	*K. pneumoniae*	Prophage/LysECD7	diffusion chambers implanted in outbred rats	Substantial number of viable bacteria in the formed biofilms was disrupted by 50 μg of LysECD7 injected intraperitoneally
Idelevich et al., 2020	*S. aureus*	HY-133 (chimeric lysin)	Vascular graft surface	HY-133 on graft surface-adherent cells was moderate
Schuch et al., 2017	*S. aureus*	Bacterial specific phage/CF-301	Surgical mesh, catheters	In catheters, CF-301 removed all biofilm within 1 h Antibiofilm activity of CF-301 was improved in combinations with lysostaphin Highly effective for destroying biofilms and biofilm bacteria
Yang et al., 2017	*S. aureus*	187, bacterial specific phage/ ClyF (chimeric lysin)	Mouse model of burn wound	ClyF treated burn wounds showed clear degradation of biofilm compared with control group
Yang et al., 2016	*Streptococcus mutans (S. mutans)*	Prophage/ClyR (chimeric lysin)	hydroxyapatite disks	Biofilms formed on hydroxyapatite disks (representing the tooth enamel) reduced by ~1 log at 50 μg/ml, ~2 logs at 100 μg/ml, and ~3 logs at 200 μg/ml
Thandar et al., 2016	*A. baumannii*	P307 and P307SQ-8C (engineered lysins)	polyvinyl chloride (PVC) catheter tubing	After 2 h, approximately 3- and 4-log decreases in CFU/ml were observed with P307 and P307SQ-8C After 24 h, an additional ~1.3-log decrease was observed with P307
Lood et al., 2015	*A. baumannii*	Prophage/PlyF307	Catheters, mouse model	Catheters treated with PlyF307 displayed an approximately 1.6-log-unit decrease in the number of *A. baumannii* Mouse models treated with PlyF307 displayed an approximately 2-log-unit decrease in bacterial viability
Yang et al., 2014	*S. aureus*	ClyH (chimeric lysin)	96-well plates	ClyH treated clinical S. aureus isolates showed a > 60% biofilm mass reduction

Dispersin B Therapy of Staphylococcus aureus Experimental Port-Related Bloodstream Infection

Del Pozo et al., ICAAC 2007



Experiencia clínica

2023

Bactériophages et chirurgie orthopédique. A propos de sept cas

Lang, G. et al., J. Bactériophages et chirurgie orthopédique 1979

Box 2. Conclusion of Lang et al. 1979 [109].

Seven orthopedic surgery cases were treated with bacteriophages between 1975 and 1976. Of the treated patients, six were male and one was female. The age of patients ranged from 19–70 years of age. The cases presented by authors were chronic, having exhausted the usual therapeutic arsenal, and phage was added to other treatments in order to maximize patient benefit.

Five treatments resulted in good clinical outcomes, which was supported by radiological and bacteriological examination. A condition was considered improved if symptoms were ameliorated and radiological examination was positive, but problems persisted with scarring and positive bacterial cultures (one case). Treatment failure with added phages occurred for one patient and caused a change in treatment plan, comprising first local and general antibiotic therapy (ampicillin, cephalosporin, gentamicin), then hyperbaric oxygen therapy, and finally surgical intervention, which ultimately resulted in a favorable outcome. In conclusion, the use of suitable bacteriophages in the treatment of antibiotic-resistant chronic bone infections seemed to be an interesting therapeutic alternative for authors, and the results of these cases encouraged continuation in this therapeutic direction.

Phage therapy: From biological mechanisms to future directions

Steffanie A. Strathdee et al., Cell 2022

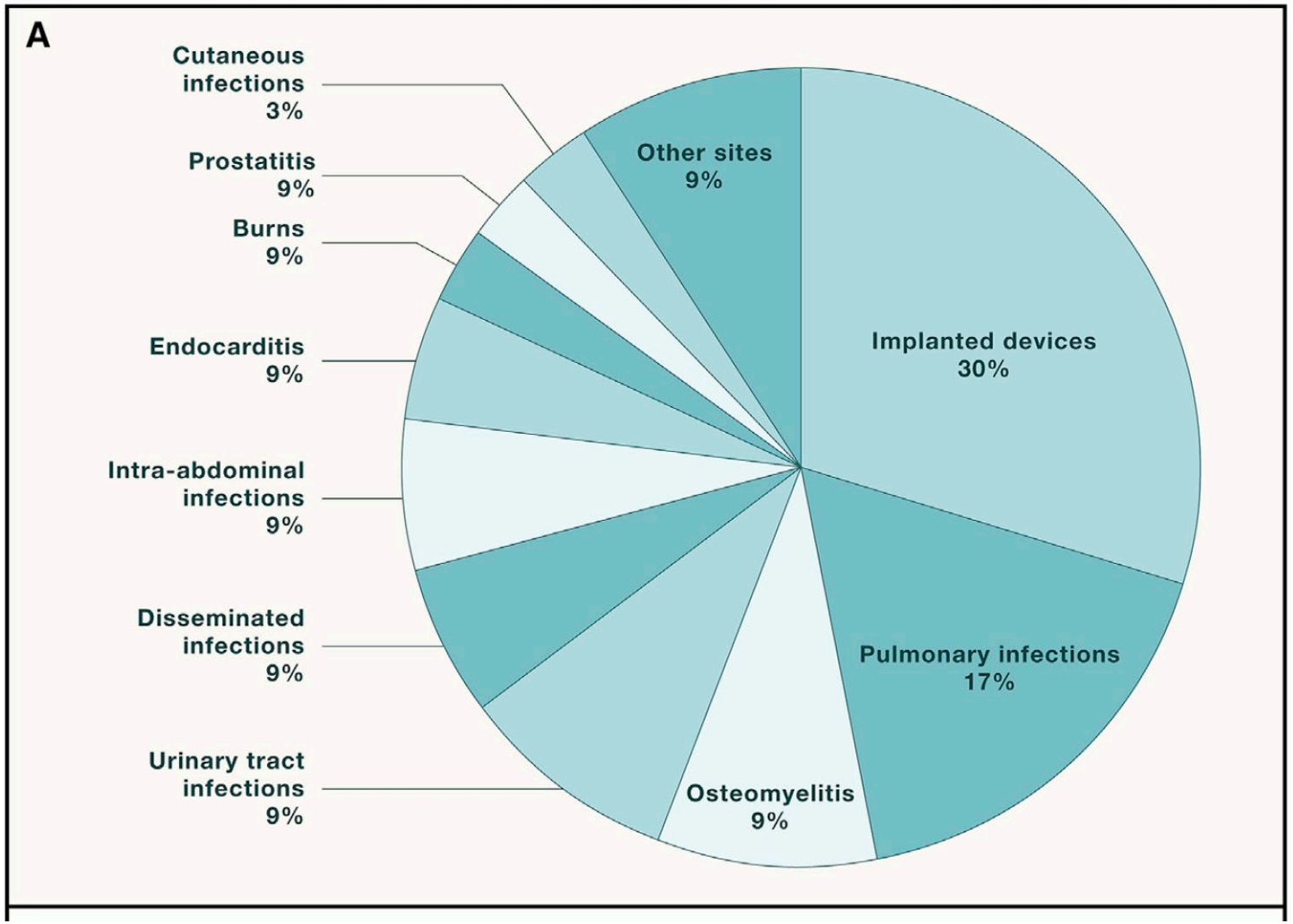


Figure 2. Phage therapy reports and phage studies by year listed

(A) Case reports of phage therapy since 2000. A PubMed search was performed on September 22, 2022, using the search terms "(bacteriophage) AND (therapy) AND (case report)." Sites of infection in each of the 70 cases reported in 53 manuscripts are depicted.

2023

Biological challenges of phage therapy and proposed solutions: a literature review

Katherine M Caflisch et al., Expert Review of Anti-infective Therapy 2019

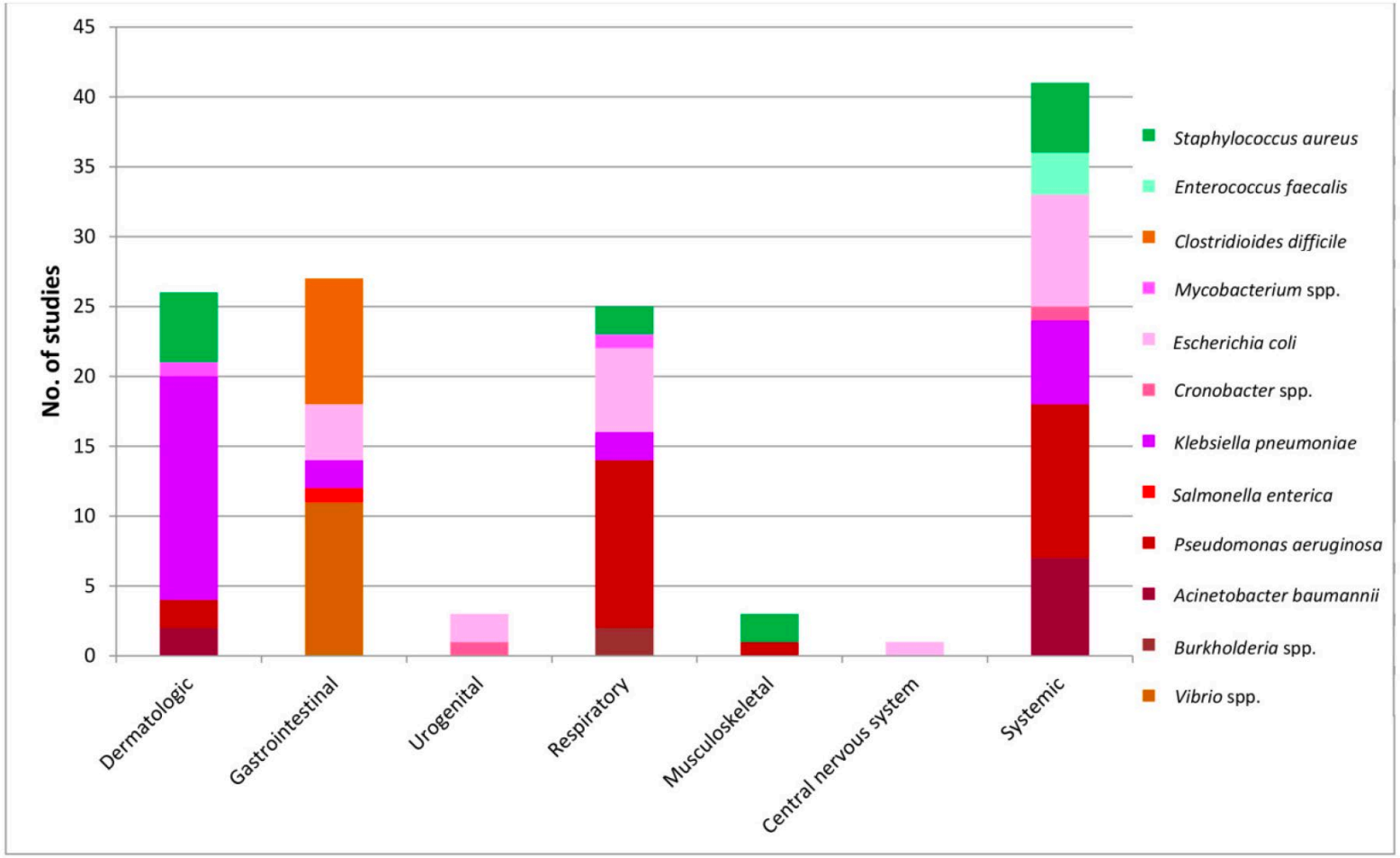


Figure 2. *In vivo* phage efficacy studies published between January 1, 2007 and October 21, 2019, by infection and bacterial type.

Biological challenges of phage therapy and proposed solutions: a literature review

Katherine M Caflisch et al., Expert Review of Anti-infective Therapy 2019

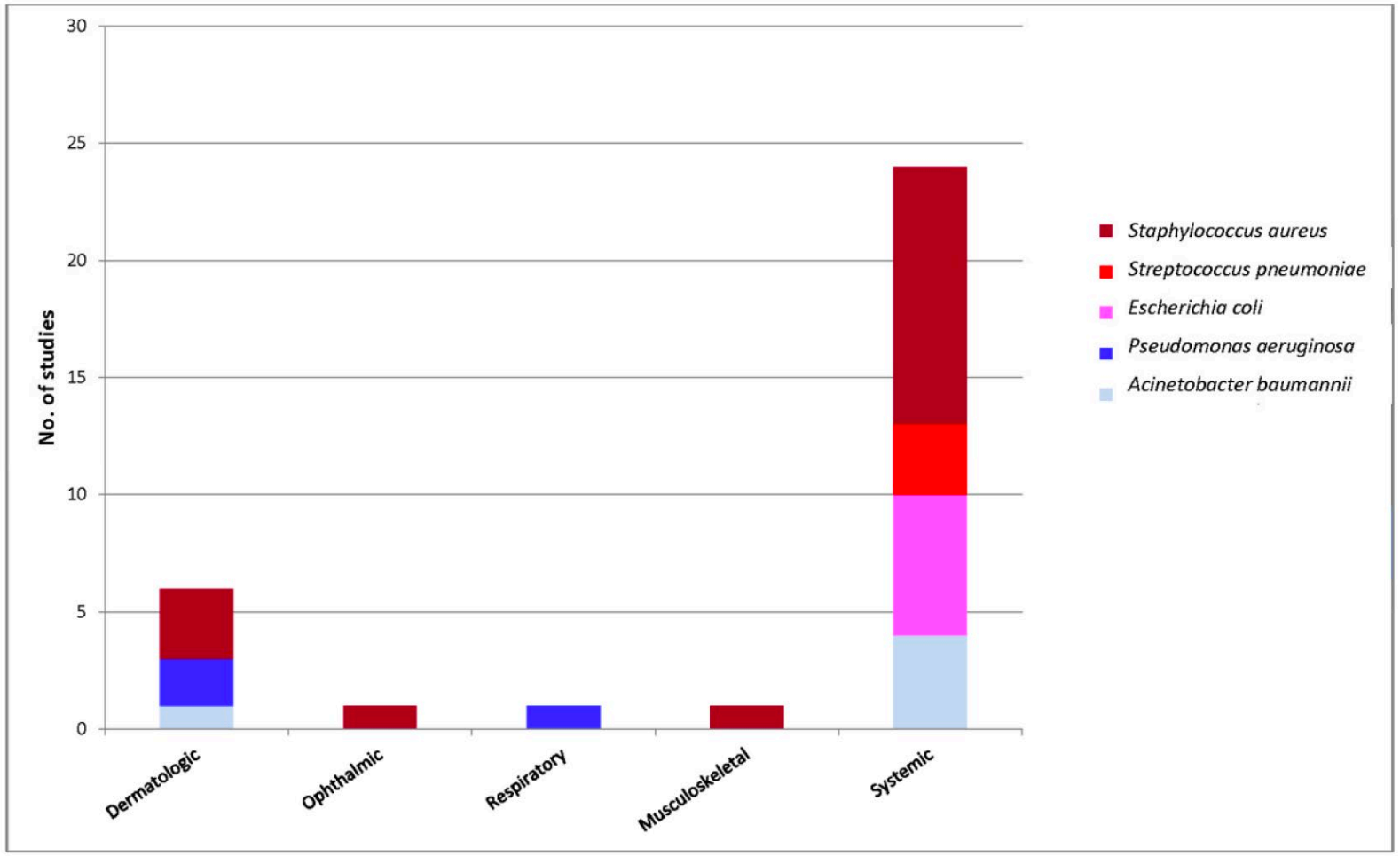
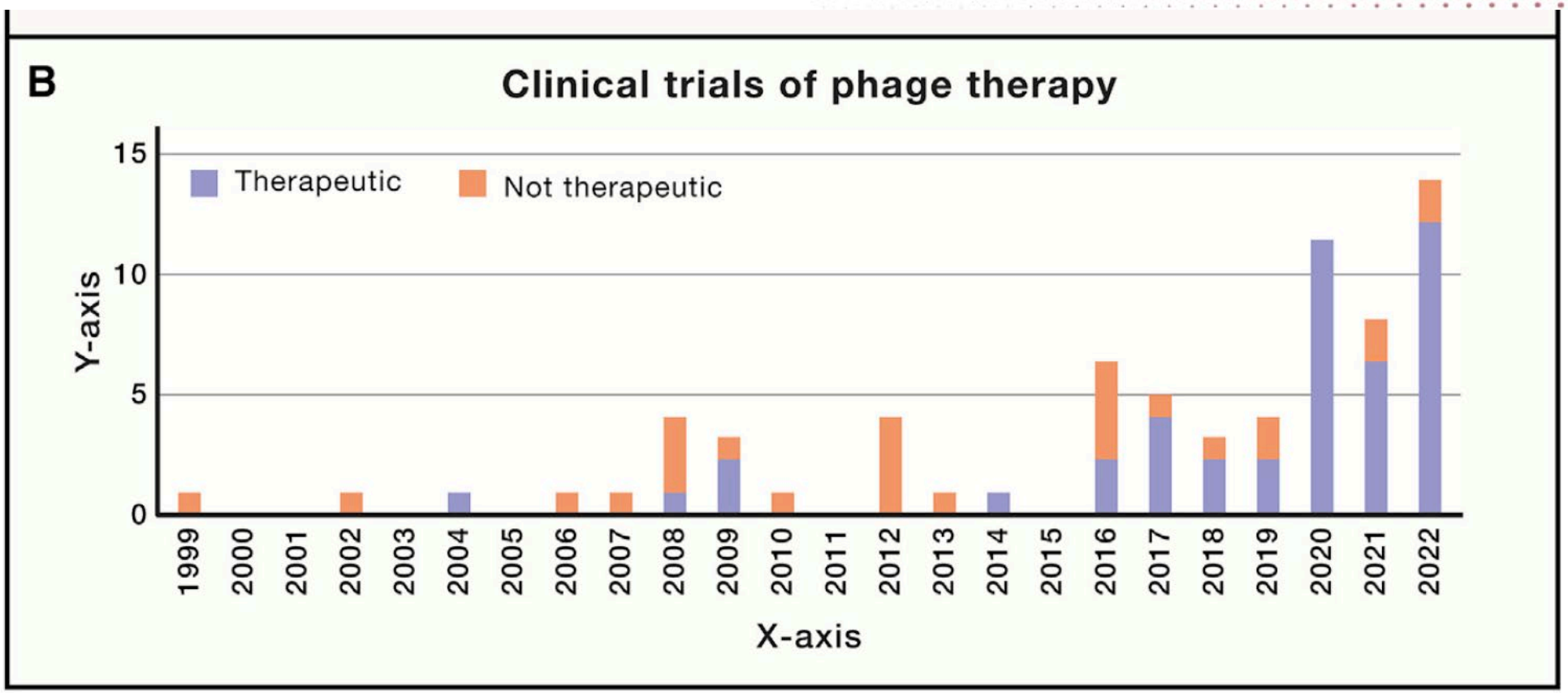


Figure 3. *In vivo* lysin efficacy studies published between January 1, 2007 and October 21, 2019, by infection and bacterial type.

Phage therapy: From biological mechanisms to future directions

Steffanie A. Strathdee et al., Cell 2022



(B) Clinical trials of phage therapy reported to ClinicalTrials.gov since 1999. The registry was queried using the key word "phage" on September 9, 2022.

Essential Topics for the Regulatory Consideration of Phages as Clinically Valuable Therapeutic Agents: A Perspective from Spain

Roberto Vázquez et al., Microorganisms 2022

Table 1. Ongoing clinical trial examples involving phage therapy.

Disease	Pathogen(s)	Treatment	Status	References
Diabetic foot ulcers	*Staphylococcus aureus*	Topical phage cocktail	Not yet recruiting (expected start date: June 2022)	NCT02664740
Invasive infection in patients with inactive Crohn's disease	*E. coli*	Oral phage cocktail	Recruiting (estimated completion: June 2023)	NCT03808103
Chronic airway infection in cystic fibrosis patients	*P. aeruginosa*	Nebulized phage therapy	Recruiting (estimated completion: December 2022)	NCT04684641
Diabetic foot ulcers	*P. aeruginosa*, *S. aureus* and/or *Acinetobacter baumannii*	Topical phage cocktail	Recruiting (estimated completion: December 2021	NCT04803708
Prosthetic joint infections	Several pathogens	Combined antibiotic/personalized phage therapy	Not yet recruiting (estimated start date: October 2022)	NCT04787250
Chronic airway infection in cystic fibrosis patients	*P. aeruginosa*	Nebulized phage cocktail	Not yet recruiting	NCT05010577
Wound infections in burned patients	*S. aureus*, *P. aeruginosa* or *Klebsiella pneumoniae*	Topical phage cocktail	Not yet recruiting (estimated start date: January 2022)	NCT04323475
Pressure injury infections	*S. aureus*, *P. aeruginosa*, *K. pneumoniae*	Topical phage cocktail in combination with antibiotics	Not yet recruiting (estimated start date: January 2022)	NCT04815798
Urinary tract infections	*E. coli* or *K. pneumoniae*	Personalized phage therapy administered through intravenous or intravesical route	Recruiting (estimated completion: September 2023)	NCT04287478
Tonsillitis	Several pathogens	Nebulized phage cocktail	Phase 3. Active, not recruiting (estimated completion: December 2024)	NCT04682964
Chronic airway infection in cystic fibrosis patients	*P. aeruginosa*	Inhaled phage cocktail	Recruiting (estimated completion: March 2022)	NCT04596319

A systematic review of phage therapy applied to bone and joint infections: an analysis of success rates, treatment modalities and safety

Joseph Geneviève et al., EFORT Open Rev 2021

Table 1. Level of evidence of each record

Ref.	Number of patients included	Level of evidence
Ramirez-Sanchez et al[26]	1	Case report
Ferry et al[27]	1	Case report
Doub et al[24]	1	Case report
Ferry et al[28]	3	Case series
Nadareishvili et al[29]	3	Case series
Ferry et al[30]	1	Case report
Cano et al[31]	1	Case report
Doub et al[25]	1	Case report
Tkhilaishvili et al[32]	1	Case report
Onsea et al[33]	4	Case series
Nir-Paz et al[34]	1	Case report
Patey et al[35]	9	Case series
Ferry et al[36]	1	Case report
Fish et al[37]	1	Case report
Ferry et al[38]	1	Case report
Fish et al[39]	5	Case series
Efremov et al[40]	1	Case report
Vogt et al[41]	1	Case report
Samokhin et al[42]	12	Cohort study
Fish et al[43]	2	Case series

A systematic review of phage therapy applied to bone and joint infections: an analysis of success rates, treatment modalities and safety

Joseph Geneviève et al., EFORT Open Rev 2021

Table 2. Summary of patient characteristics and treatment episodes

Age (years), mean (*SD*)	63.0 (24.8) [of 47 patients]
Sex male, *n* (%)	23/46 (50) [of 46 patients]
Localization (per treatment episode), *n*[a] (%)	
- Hip	14/52 (27)
- Knee	14/52 (27)
- Toes	8/52 (15)
- Femur	5/52 (10)
- Tibia	5/52 (10)
- Pelvis	3/52 (6)
- Foot	2/52 (4)
- Other*	3/52 (6)
Pathogens (per treatment episode), *n*[a] (%)	
- *Staphylococcus aureus*	30/52 (58)
- *Staphylococcus epidermidis*	13/52 (25)
- *Pseudomonas aeruginosa*	9/52 (17)
- Staphylococci other than *S. aureus* and *S. epidermidis***	2/52 (4)
- Other***	5/52 (10)
Diagnostics (per treatment episode) [b]	
- PJI	28/52 (54)
- Osteomyelitis (including FRI)	24/52 (46)
Phage specificity testing (per treatment episode)[c]	43/52 (83)
Administration route (per treatment episode), *n* (%)	
- **Topical only**	**44/52 (85)**
- **IV only**	**2/52 (4)**
- **Topical and IV**	**3/52 (6)**
- **Topical and PO**	**3/52 (6)**
- *Topical IOIA*	*39/52 (75)*
- *Topical sup.*	*11/52 (21)*
Combined surgery before or during PT (per treatment episode), *n* (%)	**45/52 (87)**
Combined antibiotics with PT (per treatment episode), *n* (%)	**41/52 (79)**
Combined surgery and antibiotics with PT (per treatment episode), *n* (%)	**39/52 (75)**
Outcome (per treatment episode), *n* (%)	
- **A**	**37/52 (71)**
- **B**	**2/52 (4)**
- **C**	**7/52 (13)**
- **D**	**2/52 (4)**
- **E**	**4/52 (8)**
- *1 (B1, C1 and D1)*	*6/52 (12)*
- *2 (B2, C2 and D2)*	*5/52 (10)*
Success (per treatment episode), *n* (%)	**37/52 (71)**
Failure (per treatment episode), *n* (%)	**15/52 (29)**
Positive outcome A + 1 (per treatment episode), *n* (%)	**43/52 (83)**
Follow-up (per treatment episode) time (months), mean (*SD*), range	11.9 (9.4) 1.5–41.0 [of 39 treatment episodes]
Reports of AE linked to PT (per treatment episode), *n* (%)	4/52 (8)
Patients with SAT initiated during or after PT (per treatment episode), *n* (%)	8/36 (22) [of 36 treatment episodes]

A systematic review of phage therapy applied to bone and joint infections: an analysis of success rates, treatment modalities and safety

Joseph Geneviève et al., EFORT Open Rev 2021

Table 3. Adverse events (AEs)

Ref.	Number of treatment episodes	Reports of AEs considered to be linked to PT and therapeutic consequence if applicable	Reports of other AEs or comorbidities
Ferry et al[27]	1	–	Death due to lithiasic pancreatitis after 1 year ($n = 1$)
Doub et al[24]	1	Elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) the day following topical PT → IV PT not administered ($n = 1$)	–
Ferry et al[30]	1	–	Myocardial infarction, uncontrolled bleeding ($n = 1$)
Cano et al[31]	1	Minor and intermittent pruritus of the right lower extremity 2 weeks into the course of therapy and slight elevation of TNF-alpha after PT ($n = 1$)	–
Doub et al[25]	1	Elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) after third IV dose → IV PT discontinued ($n = 1$)	–
Onsea et al [33]	4	Local redness and pain during rinsing procedure after 7 days of treatment ($n = 1$)	–
Ferry et al[38]	1	–	Death due to oncological comorbidity ($n = 1$)
Vogt et al[41]	1	–	Stiffening of two large joints of a leg with corresponding functional deficit ($n = 1$)

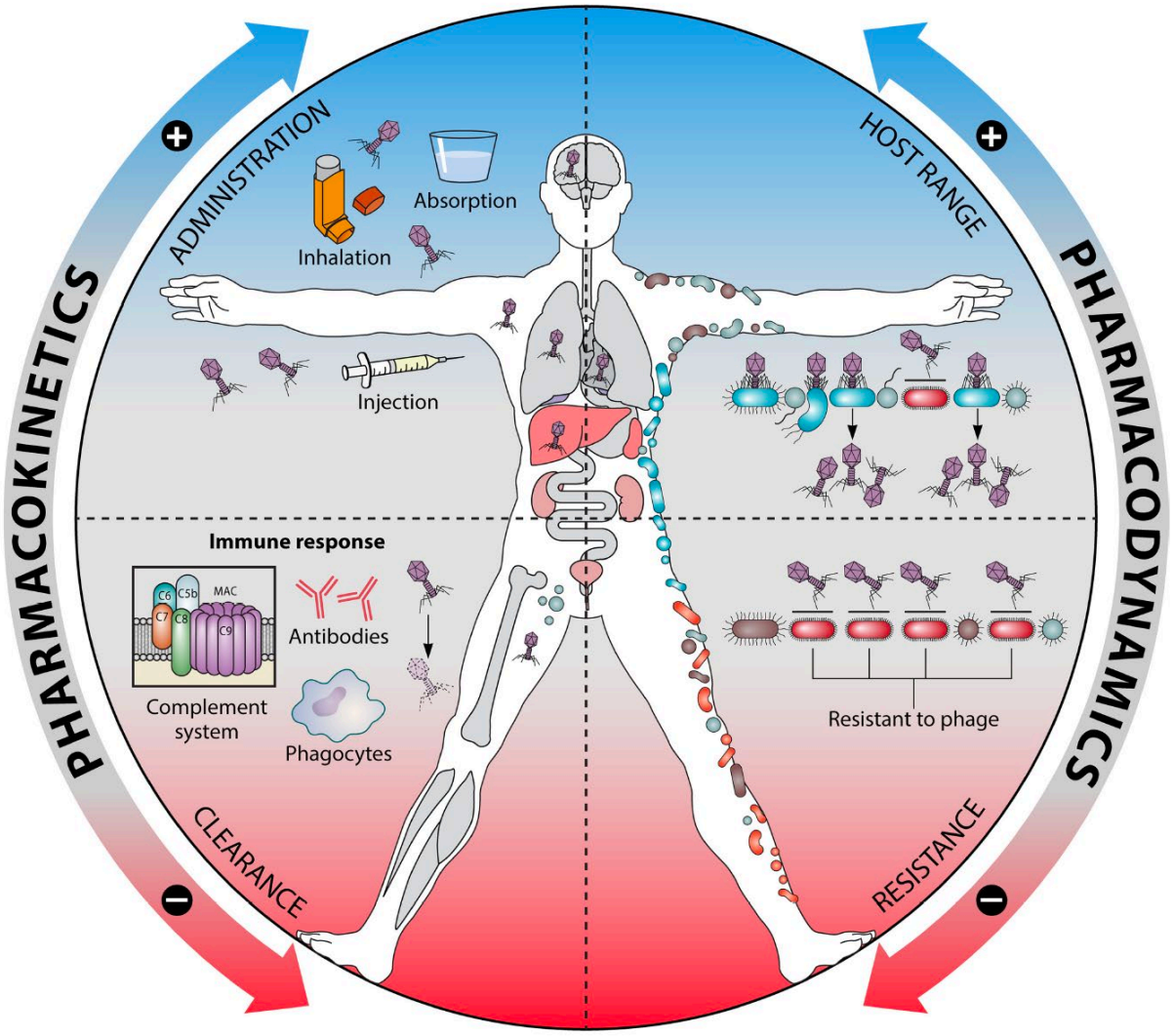
Notes. Ref., reference; AE, adverse events; PT, phage therapy; –, not reported; IV, intravenous.

Limitaciones al uso de fagoterapia

2023

Pharmacologically Aware Phage Therapy: Pharmacodynamic and Pharmacokinetic Obstacles to Phage Antibacterial Action in Animal and Human Bodies

Krystyna Da˛browska,et al., Microbiology and Molecular Biology Reviews 2019

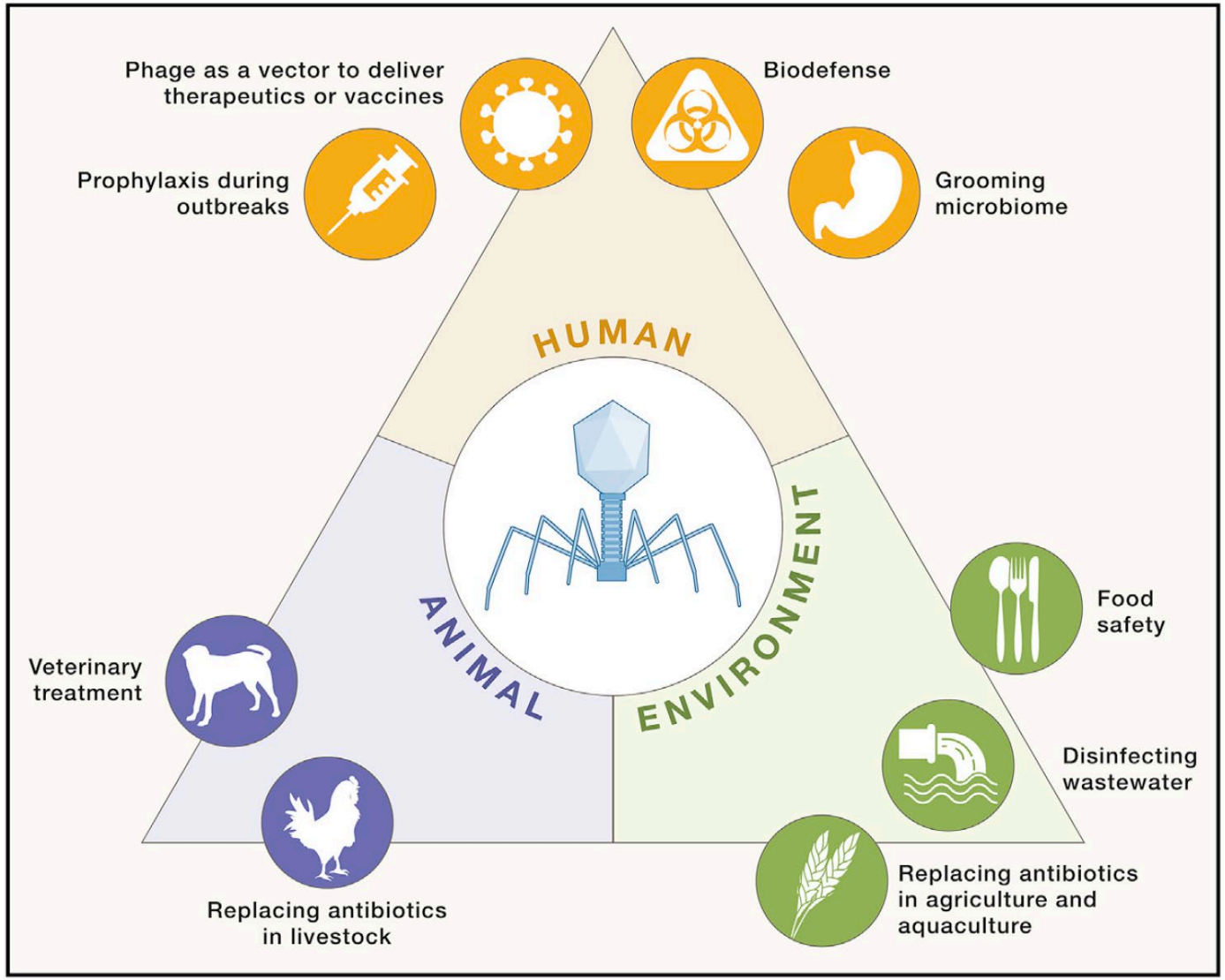


El futuro

2023

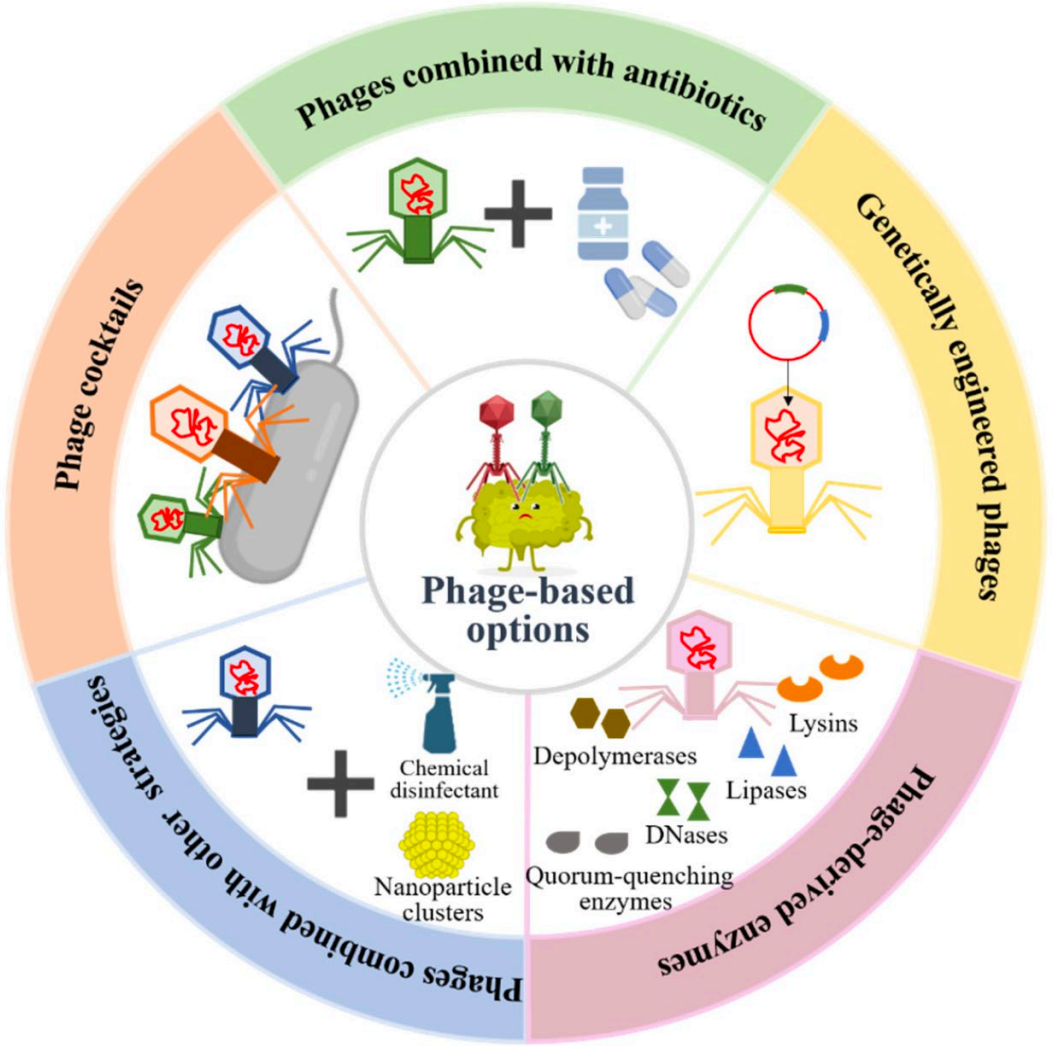
Phage therapy: From biological mechanisms to future directions

Steffanie A. Strathdee et al., Cell 2022



Phages against Pathogenic Bacterial Biofilms and Biofilm-Based Infections: A Review

Siyu Liu et al., Pharmaceutics 2022



Phage therapy: From biological mechanisms to future directions

Steffanie A. Strathdee et al., Cell 2022

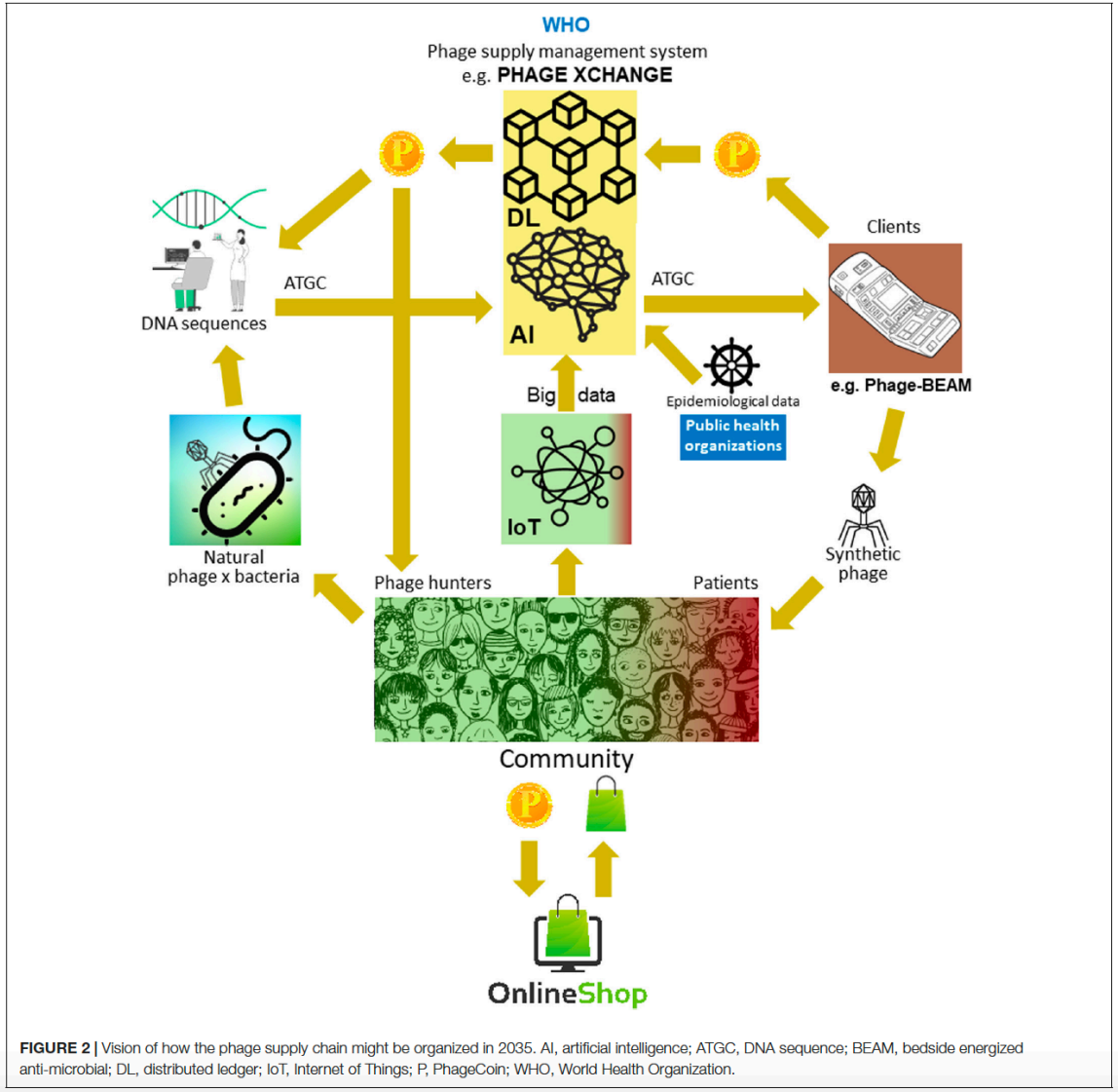


FIGURE 2 | Vision of how the phage supply chain might be organized in 2035. AI, artificial intelligence; ATGC, DNA sequence; BEAM, bedside energized anti-microbial; DL, distributed ledger; IoT, Internet of Things; P, PhageCoin; WHO, World Health Organization.

The Israeli Phage Bank (IPB)

Ortal Yerushalmy et al., Antibiotics 2020

Table 1. Phage collections worldwide.

Phage Collection Name	Number of Phages	Hosts	Link
Adaptive phage therapy (APT) phage bank	~1000	Mainly the ESKAPE pathogens	http://www.aphage.com/the-science/
The Felix d'Hérelle Reference Center for Bacterial Viruses	>400	A few dozen hosts	https://www.phage.ulaval.ca/en/phages-catalog/
The Bacteriophage Bank of Korea	~1000	A few dozen hosts	http://www.phagebank.or.kr/intro/eng_intro.jsp
Leibniz Institute—DSMZ (German Collection of Microorganisms and Cell Cultures)	~300	Unknown	https://www.dsmz.de/collection/collection-experts
ATCC Bacteriophage Collection	~400	A few dozen hosts	https://www.atcc.org/search#q=phage&sort=relevancy&f:productcategoryFacet=[Bacteria%20%26%20Phages]&f:listofapplicationsFacet=[Bacteriophage]
NCTC Bacteriophage Collection	>100	*Streptococcus* ssp *Staphylococcus* ssp *Campylobacter*	https://www.phe-culturecollections.org.uk/products/bacteria/bacteriophages.aspx
Hatfull Lab Phage Collection	>15,000	Species from Actinobacteria phylum	https://phagesdb.org/ http://www.hatfull.org/sea-phages
TUDelft	Unknown	Unknown	https://www.tudelft.nl/en/delft-university-fund/
P.H.A.G.E	Unknown	Unknown	http://www.p-h-a-g-e.org/
Israeli Phage Bank (IPB)	>300	16 different species	https://ronenhazanlab.wixsite.com/hazanlab/the-404-israeli-phage-bank

The Israeli Phage Bank (IPB)

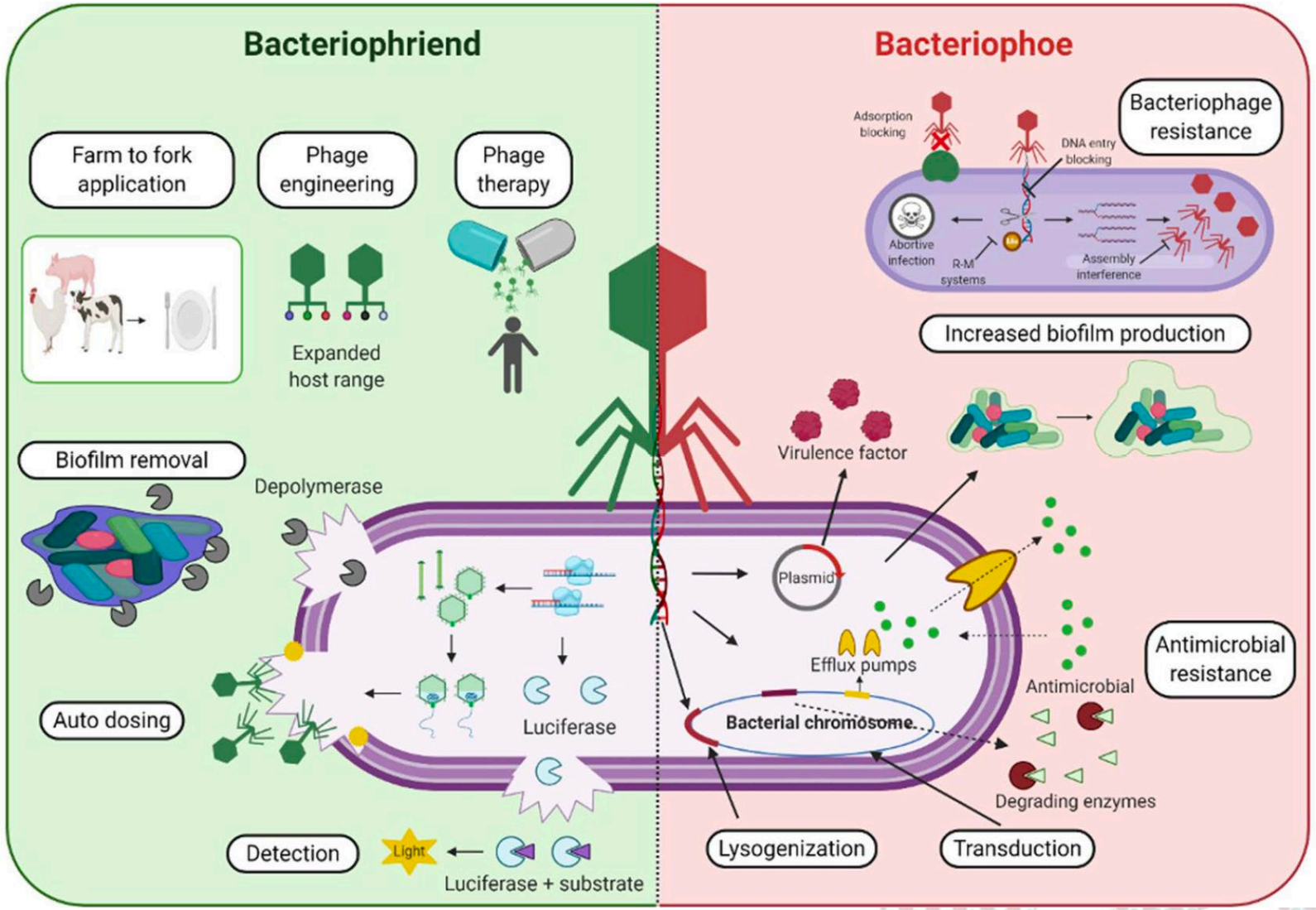
Ortal Yerushalmy et al., Antibiuotics 2020

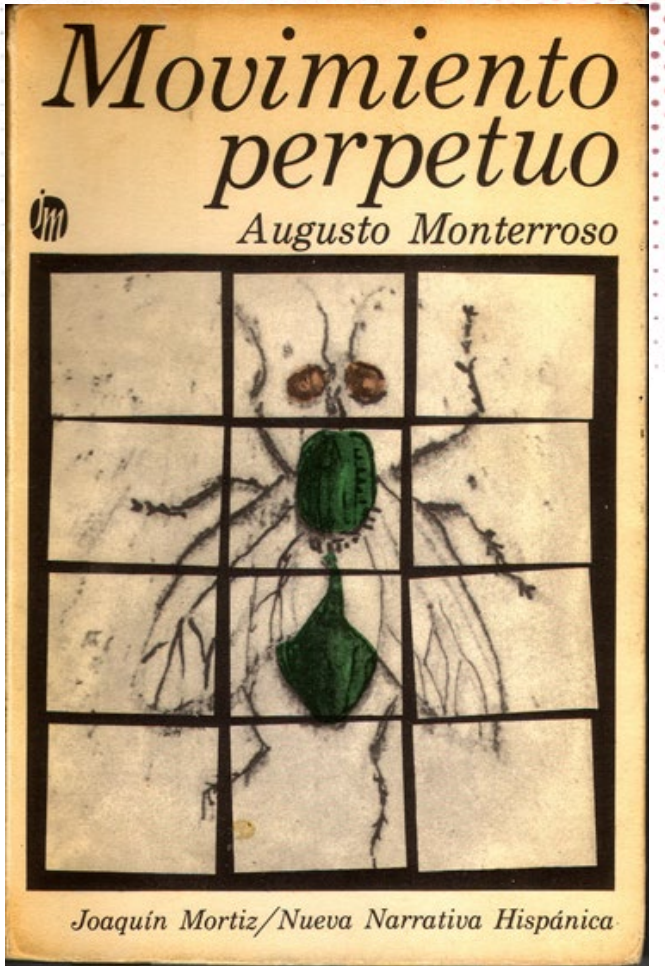
Table 3. Phage collection.

Bacteria Strain	Clinical Strains	Phages	Percentage of Coverage	Minimum Phages Require for Coverage
Staphylococcus aureus	20	25	100%	1
Klebsiella pneumoniae	8	30	100%	2
Pseudomonas aeruginosa	100	54	100%	9
Pseudomonas stutzeri	2	6	100%	1
Enterobacter spp	7	20	100%	3
Burkholderia spp	23	15	90%	5
Burkholderia lata	1	2	100%	1
Enterococcus faecalis + *Enterococcus faecium*	8	38	100%	1
Streptococcus mutans	15	1	100%	1
Acinetobacter baumannii	8	19	100%	2
Propionibacterium acnes	36	22	86%	1
Providencia spp	35	10	100%	3
Escherichia coli	5	25	100%	1
Bacillus anthracis	1	6	100%	1
Salmonella	30	1	100%	1
Shigella	2	12	100%	1
Mycobacterium abscessus	6	3	100%	1
Total	**307**	**289**	**97%**	**35**

The Age of Phage: Friend or Foe in the New Dawn of Therapeutic and Biocontrol Applications?

Hassan, A.Y.; et al., Pharmaceuticals 2021





Y como lo observan los naturalistas, una mosca tiene moscas más pequeñas que la devoran, y éstas tienen otras más pequeñas todavía que las muerden, y así ad infinitum.
Jonathan Swift

Gracias!

Clínica Universidad de Navarra

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