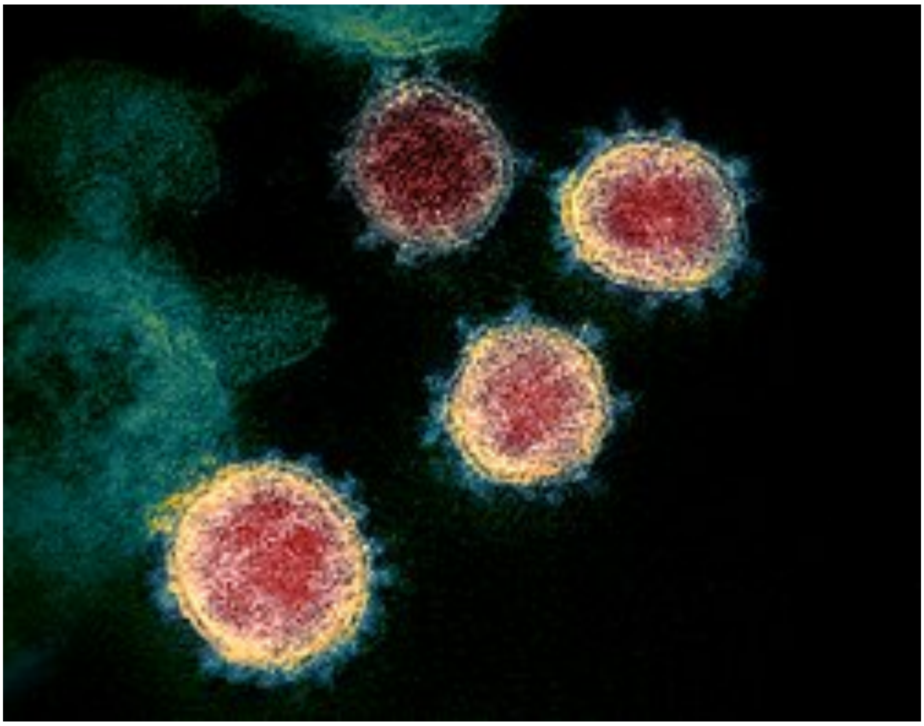
Microbial disease due to infection by viruses

Sanne Wolput[1], Maarten Boon[1], Hanne Hendrix[1], Ines Staes[2], Bob Blasdel[1], Kiandro Fortuna[1], Dominique Holtappels[1], Angela Makumi[2], Jolien Onsea[3,4], Oscar Enrique Montaguth Torres[2], Jeroen Wagemans[1], Jan Paeshuyse[5] and Rob Lavigne[1]

[1]KU Leuven, Department of Biosystems, Laboratory of Gene Technology, [2]KU Leuven, Department of Microbial and Molecular Systems, Laboratory of Food Microbiology, [3]KU Leuven, Department of Development and Regeneration, Locomotoric and neurological disorders, [4]University Hospitals Leuven, Department of Trauma Surgery, [5]KU Leuven, Department of Biosystems, Laboratory of Host Pathogen Interaction in Livestock, Leuven, Belgium



Microscope image showing the SARS-CoV-2 virus (source: Wikipedia)

Microbial disease due to infection by viruses

Microbial disease due to infection by viruses: the Microbiology

1. ***Ecological impact of phages.*** Bacteriophages or phages are prokaryotic viruses that infect bacteria. The first indications hinting their existence date back to the end of the 19th century. Ernest Hankin, an English bacteriologist, reported bactericidal properties of the waters of the Jamuna and Ganges rivers in Allahabad, India. These rivers were known for their curative power against infections, including cholera bacteria. Analysis of the water indicated an unexpected low number of bacteria. This reduced bacterial count could not be explained by the absence of polluting factories or concentrated villages in the proximity of the rivers, since the latter received water from drains from a nearby city that did contain Cholera bacteria. Further research showed that the antibacterial properties were lost upon heating. Hankin hypothesized that the water contained an unknown antiseptic substance that was formed in the river or formed *in situ* by the water, and that was able to kill Cholera microbes in less than three hours. Current indications still question whether these observations were indeed phage-related.

Two decades later, the presence of bacteriophages on the planet was definitively proven. The British pathologist Twort described in 1915 “glassy and transparent” spots of dead bacteria. These clear spots were transmissible and specific to the bacterial type he was aiming to grow. In 1917, Felix d’Hérelle independently showed similar results. This French-Canadian microbiologist isolated an “anti-microbe” of *Shigella dysenteriae*. He interpreted his observations as intracellular parasitism and introduced the term bacteriophage, literally meaning “bacteria-eater”, as derived from the Greek language. D’Hérelle is therefore considered as the pioneer of bacteriophage research. Moreover, he acknowledged the importance of Hankin’s earlier results. The lethal effect of phages was first proposed as an antibacterial strategy by Bruynoghe and Maisin in 1921. As such, d’Hérelle cooperated with a Georgian microbiologist, George Eliava, and implemented the first phage therapy center in 1923. This institute is still known as the center of phage therapy in Europe to date and was named after its founder: the George Eliava Institute of Bacteriophage, Microbiology and Virology in Tbilisi, Georgia.

Over the next twenty years leading up to World War II, several phage-based treatments for bacterial infections were developed. However, the discovery and the success of antibiotics led to a decline of medical bacteriophage research in Western Europe. Meanwhile, this research did continue in Eastern European countries, including Georgia and Poland. Nevertheless, the fast spread of antibiotic resistant bacteria resulted in a renewed interest in phage therapy in the West. Some important milestones from the past 100 years of phage research are summarized on Figure 1.

Con forma

Con forma

Eliminado

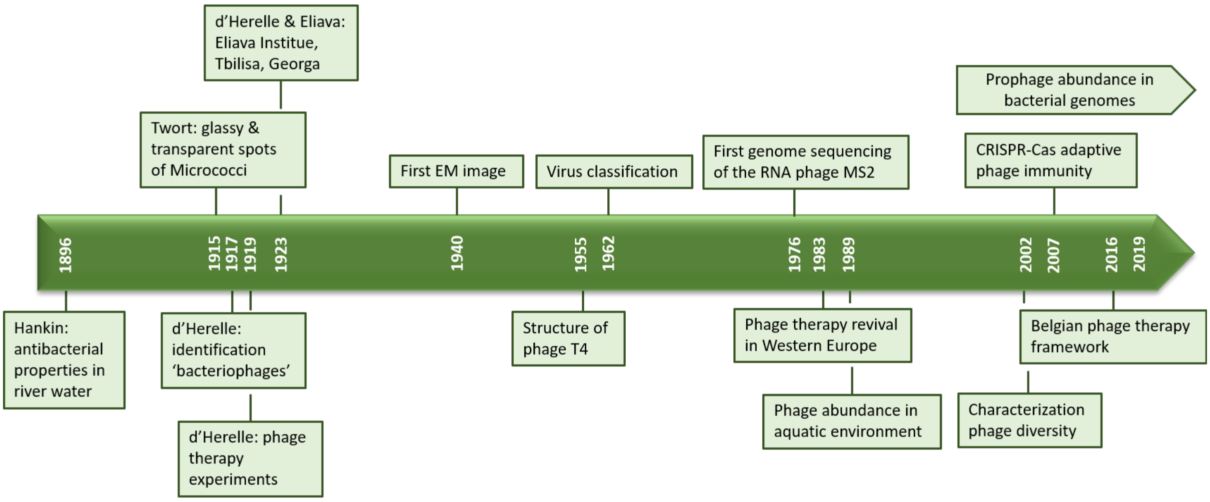


Figure 1. An overview of major milestones of phage research. Highlights are the antibacterial properties in Indian river water (Hankin; 1896), leading to the discovery of bacteriophages by Twort and d'Herelle (1915-1917); the revival of phage therapy in Western Europe from the '80s; the characterization of CRISPR-Cas adaptive phage immunity (2007) and the establishment of a Belgian phage therapy framework in 2016. Other milestones can be found on the timeline.

A century of phage research has made it clear that phages are the most abundant organisms on the planet, with an estimated 10^{31} viral particles present in our biosphere. Phages isolated from various environments have been deeply studied, including soil, lakes, sewage and oceans. Aquatic ecosystems contain 15-fold more phages than bacteria. Moreover, phages appear to kill and lyse between 10% and 30% of the ocean's bacteria every day, indicating the major effect they have on ecology and microbial populations. The dynamics of algal blooms suddenly appearing and disappearing demonstrate this impact. The latter phenomenon can be explained by the vicinity of microbial viruses that serve as a natural biocontrol agent which target the algae.

The impact of bacteriophages on aquatic environments is further discussed in the 'Bacteriophages in the ocean' video (Supplementary data, V1 - Bacteriophage ecology). This video shows that bacteriophages influence the carbon storage in the ocean and thus affect the carbon cycle, which in turn alters the climate. The video also emphasizes the need to study bacteriophages and the interactions with their host to gain important insights in bacteriophage biology and its biotechnological exploitation.

2. Biology of microbial viruses

a. Diversity. Bacteriophages demonstrate remarkable diversity. Virions of various size, shape and complexity can be found. Viral genomes vary enormously in size, ranging from 3.4 kb to 500 kb, and contain mosaic patterns, *i.e.* genetic modules that appear in diverse combinations. According to the National Center for Biotechnology Information (NCBI); 3,543 complete phage genomes have been sequenced (January 2021). However, it is estimated that over ten million phage species exist in nature, so the current understanding of phage diversity is still limited. Detailed information of viral diversity and genome characteristics can be found in the 'Bacteriophage genomes' video (Supplementary data, V2 – Bacteriophage genomes).

The different types of phages are currently classified into 13 families, based on the genomic material (single or double stranded DNA or RNA), morphology and genome organization. The morphology of the bacteriophage is usually specific to the different families. However, most are composed of a nucleic acid molecule and a proteinaceous capsid surrounding the genetic material although some lipid-containing phages exist. The capsid can be icosahedral, filamentous, and/or head-tail in shape (Figure 2). The tailed bacteriophages have tail fibers to bind to the bacterial surface with high specificity. Among the tailed bacteriophages, the length and flexibility of the tail can vary and a collar can be either absent or present. Most described phages have a head-tail structure and 96% of them belong to the *Myoviridae*, *Siphoviridae* or *Podoviridae* families which comprise the tailed, double stranded DNA phages.

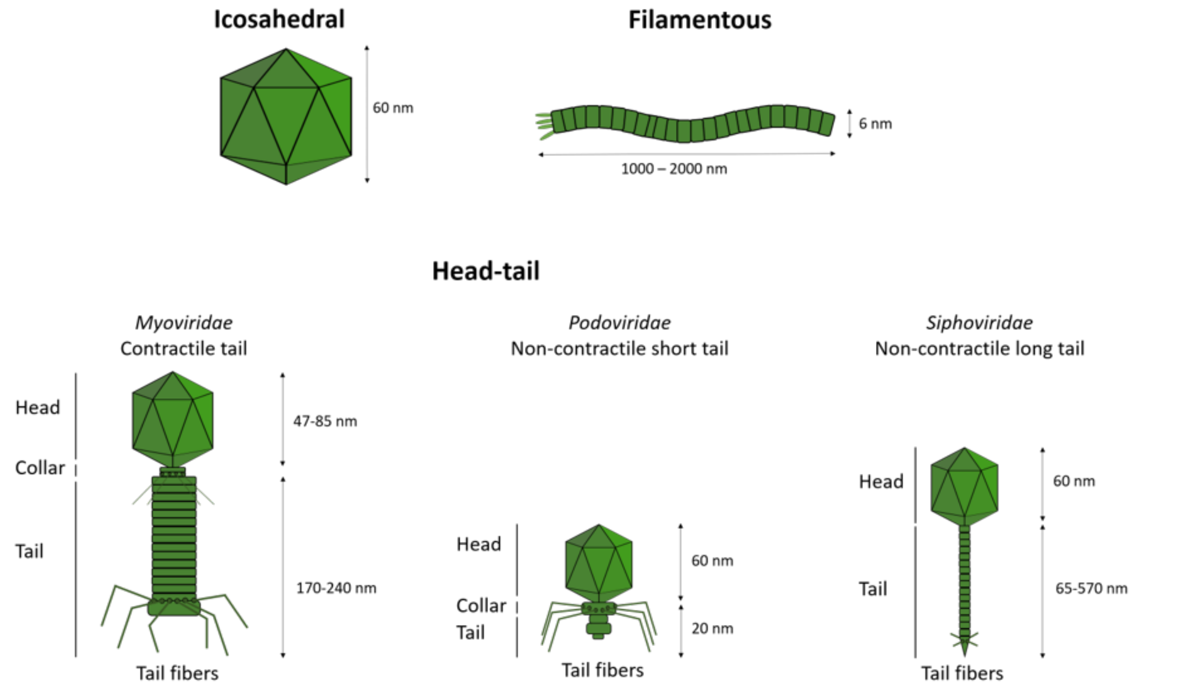


Figure 2. Bacteriophage shape. Phages are composed of a proteinaceous capsid surrounding a nucleic acid molecule. The capsid can be icosahedral, filamentous or head-tail in shape. The head-tailed phages have tail fibers, binding the surface of the host with high specificity. These phages have variable tail length and flexibility, and a collar can be absent or present.

b. Infection cycles of bacteriophages. Similar to human viruses, bacteriophages require a host cell for infection and reproduction. Depending on the type of phage, different infection cycles can occur (Figure 3). Strictly lytic or 'virulent' phages exclusively start infection by redirecting the host machinery towards virion production. This lytic infection cycle involves six different stages, starting with (1) the attachment of the phage to the host surface. The phage binds with its tail to bacterial surface receptors on the cell wall. Possible receptor targets include lipopolysaccharides, teichoic acids, proteins and flagella. After successful attachment, tailed phages inject their DNA (2) by penetrating the host cell wall. The host metabolism is redirected towards phage production (3). Generally, the host RNA polymerase, transcription factors and ribosomes are used to express early genes of the phage genome leading to the production of viral DNA polymerases and proteins required for DNA replication. Furthermore, either a DNase for the degradation of host DNA into precursor molecules or an endonuclease is expressed by some phages. The produced early proteins also regulate the viral gene expression, for example the activation of late gene transcription. In a next step, host and phage factors assemble into a phage replication complex that replicates the phage DNA. Furthermore, phage structural proteins are translated (4). Capsid proteins assemble into heads and the phage genome is linearized and packaged (5). The tail is attached to this phage capsid. In the final stage of the infection cycle, enzymatic activity weakens the bacterial cell wall, resulting in the release of cell contents (6). This so-called lysis results in the release of the newly formed phage particles in the extracellular environment, which can then infect new host cells.

Temperate phages can opt to follow either this lytic cycle or an alternative lysogenic cycle. During lysogenic development, the phage integrates its DNA into the host chromosome via recombination and becomes a prophage. The bacterial cell harbouring a phage genome is called a lysogen. The prophage synchronously replicates with the host and genes involved in the lytic cycle are repressed. In addition, genes encoding immunity factors are expressed. These factors alter the host cell to prevent infection of identical or closely related viruses, a phenomenon called superinfection exclusion. Superinfection might lead to host lysis or competition for host resources and could be detrimental for the prophage. Various mechanisms of superinfection exclusion are known: modification of the receptors on the host surface blocking phage binding, prevention of phage genome injection or expression of a protein to repress the lytic genes. The prophage remains stably present in the bacterial genome, but in the presence of altered or stressful environmental conditions (*e.g.* DNA damage by UV irradiation), the lytic cycle is initiated. The decision to commit to either lysogenic or lytic development depends on physiological conditions (*e.g.* nutrient concentration) or the ratio of phages to bacteria, which is called the multiplicity of infection (MOI).

The videos 'Overview of the bacteriophage infection cycle' and 'Lytic vs. lysogenic infection cycle' provide a more detailed and technical description of the infection cycles and demonstrate that the type of phage influences the infection cycle (Supplementary data, V3 – Overview of the bacteriophage infection cycle and V4 – Lytic vs. lysogenic infection cycle).

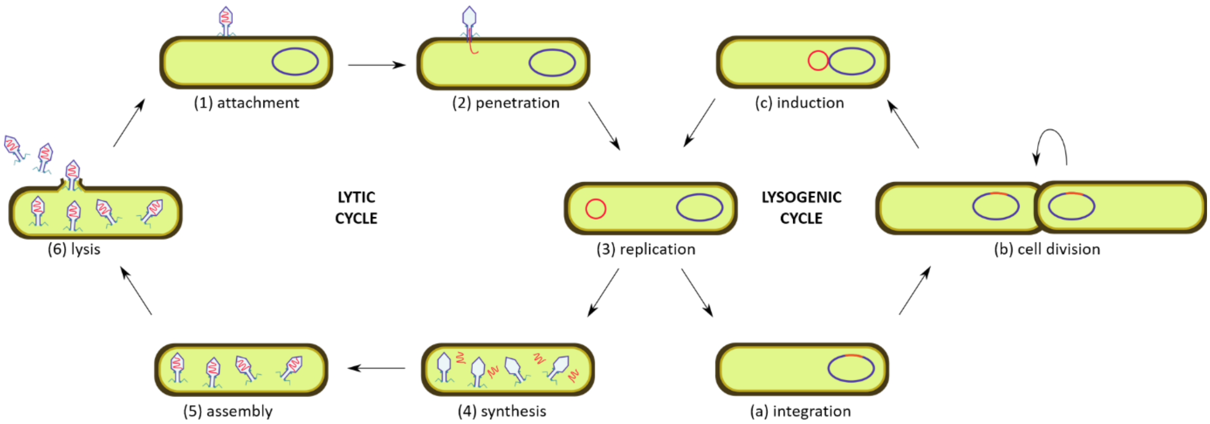


Figure 3. Infection life cycles. Two infection cycles can be distinguished. A strictly lytic or virulent phage follows the lytic cycle, resulting in virion production. The phage tail recognizes and binds to bacterial surface receptors present on the cell wall allowing successful attachment to the host cell (1). Next, the phage penetrates the cell wall, and the phage DNA is injected (2). The host metabolism is redirected towards phage production (e.g., host RNA polymerase, transcription factors and ribosomes enable the expression of early viral genes) and the phage DNA is copied during the replication stage (3). After synthesis of the structural proteins (4), the capsid proteins assemble into heads. The viral DNA is linearized and packed into the capsid heads, and the tail is attached (5). In the final stage of the infection cycle, the bacterial cell wall is weakened via enzymatic activity, which results in the burst of the bacterial host releasing phage particles in the extracellular environment. This process is called lysis (6). The newly formed virions can infect new host cells and the cycle is repeated. Temperate phages can follow this lytic cycle but can also opt to follow the lysogenic cycle. During the latter, the phage DNA is integrated in the host chromosome via recombination and becomes a prophage (a). This prophage replicates with the host during cell division (b). When environmental conditions alter (e.g. DNA damage by UV irradiation), the lytic cycle is induced (c)

3. Further reading

a. Expert reading

The following references were used to compose the 'Bacterial Viruses in Biotechnology' framework.

Abedon, S. T., Thomas-Abedon, C., Thomas, A., & Mazure, H. (2011a). Bacteriophage prehistory: Is or is not Hankin, 1896, a phage reference? *Bacteriophage*, *1*(3), 174–178. https://doi.org/10.4161/bact.1.3.16591

Abedon, S. T., Thomas-Abedon, C., Thomas, A., & Mazure, H. (2011b). Bacteriophage prehistory. *Bacteriophage*, *1*(3), 174–178. https://doi.org/10.4161/bact.1.3.16591

Abudayyeh, O. O., Gootenberg, J. S., Essletzbichler, P., Han, S., Joung, J., Belanto, J. J., Verdine, V., Cox, D. B. T., Kellner, M. J., Regev, A., Lander, E. S., Voytas, D. F., Ting, A. Y., & Zhang, F. (2017). RNA targeting with CRISPR-Cas13a. *Nature*, *550*(7675), 280–284. https://doi.org/10.1038/nature24049.RNA

Cai, W., Wang, H., Tian, Y., Chen, F., & Zheng, T. (2011). Influence of a bacteriophage on the population dynamics of toxic dinoflagellates by lysis of algicidal bacteria. *Applied and Environmental Microbiology*, 77(21), 7837–7840. https://doi.org/10.1128/AEM.05783-11

Cong, L., Ran, F. A., Cox, D., Lin, S., Barretto, R., Hsu, P. D., Wu, X., Jiang, W., & Marraffini, L. a. (2013). Cong, L., Ran, F. A., Cox, D., Lin, S., Barretto, R., Habib, N., … Zhang, F. (2013). Multiplex Genome Engineering Using CRISPR/Cas Systems. Science (New York, N.Y.). *Science*, *339*(6121), 819–823. https://doi.org/10.1126/science.1231143.Multiplex

D'Silva, M. S., Anil, A. C., Naik, R. K., & D'Costa, P. M. (2012). Algal blooms: A perspective from the coasts of India. *Natural Hazards*, *63*(2), 1225–1253. https://doi.org/10.1007/s11069-012-0190-9

Dash, P. K., Kaminski, R., Bella, R., Su, H., Mathews, S., Ahooyi, T. M., Chen, C., Mancuso, P., Sariyer, R., Ferrante, P., Donadoni, M., Robinson, J. A., Sillman, B., Lin, Z., Hilaire, J. R., Banoub, M., Elango, M., Gautam, N., Mosley, R. L., … Gendelman, H. E. (2019). Sequential LASER ART and CRISPR Treatments Eliminate HIV-1 in a Subset of Infected Humanized Mice. *Nature Communications*, *10*, 1–20. https://doi.org/10.1038/s41467-019-10366-y

Fernández, L., Escobedo, S., Gutiérrez, D., Portilla, S., Martínez, B., García, P., & Rodríguez, A. (2017). Bacteriophages in the dairy environment: From enemies to allies. *Antibiotics*, *6*(4), 1–14. https://doi.org/10.3390/antibiotics6040027

Fiers, W., Contreras, R., Duerinck, R., Haegeman, G., Iserentant, D., Merregaert, J., Min Jou, W., Molemans, F., Raeymaekers, A., Van den Berghe, A., Volckaert, G., & Ysebaert, M. (1976). Complete nucleotide sequence of bacteriophage MS2 RNA: primary and secundary structure of the replicase gene. *Nature*, *26*., 500–507. https://doi.org/10.1038/260500a0

Frangoul, H., Altshuler, D., Cappellini, D., Chen, Y.-S., Domm, J., Eustace, B. K., Foell, J., de la Fuente, J., Grupp, S., Handgretinger, R., Ho, T. W., Kattamis, A., Kernytsky, A., Lekstrom-Himes, J., Li, A. M., Locatelli, F., Mapara, M. Y., de Montalembert, M., Rondelli, D., … Corbacioglu, S. (2021). CRISPR-Cas9 Gene Editing for Sickle Cell Disease and Beta-Thalassemia. *The New England Journal of Medicine*, *384*, 252–260. DOI: 10.1056/NEJMoa2031054

Gasiunas, G., Barrangou, R., Horvath, P., & Siksnys, V. (2012). Cas9-crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(39), 2579–2586. https://doi.org/10.1073/pnas.1208507109

Gebler, C., Lohoff, T., Paszkowski-Rogacz, M., Mircetic, J., Chakraborty, D., Camgoz, A., Hamann, M. V., Theis, M., Thiede, C., & Buchholz, F. (2017). Inactivation of cancer mutations utilizing CRISPR/Cas9. *Journal of the National Cancer Institute*, *109*(1), 2015–2018.

https://doi.org/10.1093/jnci/djw183

Gomez-Lucia, E., Logue, C. H., Szyndel, M. S., & Lavigne, R. (2019). Innovative teaching in the digital age goes viral. *Nature Microbiology*, *4*(4), 562–564. https://doi.org/10.1038/s41564-019-0389-6

Grace, D. (2019). Addressing the economic burden of foodborne diseases. *International Forum on Food Safety and Trade*, 13.

Holtappels, D., Fortuna, K., Lavigne, R., & Wagemans, J. (2021). The future of phage biocontrol in integrated plant protection for sustainable crop production. *Current Opinion in Biotechnology*, *68*, 60–71. https://doi.org/10.1016/j.copbio.2020.08.016

Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J. A., & Charpentier, E. (2012). A Programmable Dual-RNA - Guided DNA Endonuclease in Adaptive Bacterial Immunity. *Science*, *337*, 816–822.https://doi.org/ 10.1126/science.1225829

Keen, E. C. (2015). A century of phage research: Bacteriophages and the shaping of modern biology. *Bioessays*, *37*(1), 6–9. https://doi.org/10.1117/12.2549369.Hyperspectral

King, A. M. Q., Adams, M. J., Carstens, E. B., & Lefkowitz, E. J. (Eds.). (2012). *Virus Taxonomy*. Elsevier.

Kochhar, R. (2020). The virus in the rivers: histories and antibiotic afterlives of the bacteriophage at the sangam in Allahabad. *Notes and Records: The Royal Society Journal of the History of Science*, *74*(4), 625–651. https://doi.org/10.1098/rsnr.2020.0019

Liang, P., Ding, C., Sun, H., Xie, X., Xu, Y., Zhang, X., Sun, Y., Xiong, Y., Ma, W., Liu, Y., Wang, Y., Fang, J., Liu, D., Songyang, Z., Zhou, C., & Huang, J. (2017). Correction of β-thalassemia mutant by base editor in human embryos. *Protein and Cell*, *8*(11), 811–822. https://doi.org/10.1007/s13238-017-0475-6

Los, M. (2011). Minimization and Prevention of Phage Infections in Bioprocesses. *Microbial Metabolic Engineering*, *834*, 305–315. https://doi.org/10.1007/978-1-61779-483-4_19

Ma, H., Tu, L. C., Naseri, A., Huisman, M., Zhang, S., Grunwald, D., & Pederson, T. (2016). CRI SPR-Cas9 nuclear dynamics and target recognition in living cells. *Journal of Cell Biology*, *214*(5), 529–537. https://doi.org/10.1083/jcb.201604115

Mali, P., Yang, L., Esvelt, K. M., Aach, J., Guell, M., DiCarlo, J. E., Norville, J. E., & Church, G. M. (2013). RNA-Guided Human Genome Engineering via Cas9. *Science*, *339*(6121), 823–826. https://doi.org/10.1126/science.1232033

Nagel, T. E., Chan, B. K., De Vos, D., El-Shibiny, A., Kang'ethe, E. K., Makumi, A., & Pirnay, J. P. (2016). The developing world urgently needs phages to combat pathogenic bacteria. *Frontiers in Microbiology*, *7*(JUN), 1–4. https://doi.org/10.3389/fmicb.2016.00882

Niu, Y., Shen, B., Cui, Y., Chen, Y., Wang, J., Wang, L., Kang, Y., Zhao, X., Si, W., Li, W., Xiang, A. P., Zhou, J., Guo, X., Bi, Y., Si, C., Hu, B., Dong, G., Wang, H., Zhou, Z., ... Sha, J. (2014). Generation of gene-modified cynomolgus monkey via Cas9/RNA-mediated gene targeting in one-cell embryos. *Cell*, *156*(4), 836–843. https://doi.org/10.1016/j.cell.2014.01.027

Onsea, J., Wagemans, J., Pirnay, J. P., Di Luca, M., Gonzalez-Moreno, M., Lavigne, R., Trampuz, A., Moriarty, T. F., & Metsemakers, W. J. (2020). Bacteriophage therapy as a treatment strategy for orthopaedic-device-related infections: Where do we stand? *European Cells and Materials*, *39*, 193–210. https://doi.org/10.22203/eCM.v039a13

Onsea, J. , Soentjens, P., Djebara, S., Merabishvili, M., Depypere, M., Spriet, I., De Munter, P., Debaveye, Y., Nijs, S., Vanderschot, P., Wagemans, J., Pirnay, J. P., Lavigne, R., & Metsemakers, W. J. (2019). Bacteriophage application for difficult-to-treat musculoskeletal infections: Development of a standardized multidisciplinary treatment protocol. *Viruses*, *11*(10). https://doi.org/10.3390/v11100891

Pereira, C., Silva, Y. J., Santos, A. L., Cunha, Â., Gomes, N. C. M., & Almeida, A. (2011). Bacteriophages with potential for inactivation of fish pathogenic bacteria: Survival, host

specificity and effect on bacterial community structure. *Marine Drugs*, *9*(11), 2236–2255. https://doi.org/10.3390/md9112236
Salmond, G. P. C., & Fineran, P. C. (2015). A century of the phage: Past, present and future. *Nature Reviews Microbiology*, *13*(12), 777–786. https://doi.org/10.1038/nrmicro3564
Sharp, R. (2001). Bacteriophages: Biology and history. *Journal of Chemical Technology and Biotechnology*, *76*(7), 667–672. https://doi.org/10.1002/jctb.434
Sulakvelidze, A., Alavidze, Z., & Morris, J. (2001). Bacteriophage therapy. *Antimicrobial Agents and Chemotherapy*, *45*(3), 649–659. https://doi.org/10.1128/AAC.45.3.649-659.2001
Teixeira, D., & Gonzalez-Pajuelo, M. (2018). Phage Display Technology for Selection of Antibody Fragments. In *Biomedical Applications of Functionalized Nanomaterials: Concepts, Development and Clinical Translation*. Elsevier Inc. https://doi.org/10.1016/B978-0-323-50878-0.00003-3
Waechter, C., Aligata, A., & Zhang, Y. (2019). *Viral Treatment of Harmful Algal Blooms*.
WHO. (2020). *Food Safety*. https://www.who.int/health-topics/food-safety

b. Recommended reading

– The online Innovirology course provides in-depth classes on bacteriophages and their biotechnological potential. The E-book, video lectures, webinars and podcasts guide you through the different topics. Available via: http://www.innovirology.com/

– Tedx Talks by Dr. Matthew Sullivan on 'The Power of Viruses, for Good'. Available via https://www.youtube.com/watch?v=4GpD8CJefL4

4. Supplementary data

The videos listed in Table 1 have been modified from the online bacteriophage course (Innovirology). Additional video's discussing related topics can be accessed via http://www.innovirology.com/media/resources/eLearning/bacteriophages/story_html5.html

Table 1. Overview of the 'Bacterial Viruses in Biotechnology' video lectures

Video title
V1 – Bacteriophage ecology
V2 – Bacteriophage genomes
V3 – Overview of the bacteriophage infection cycle
V4 – Lytic vs. lysogenic infection cycle
V5 – Phage therapy
V6 – Phage biocontrol
V7 – Bacteriophages as a threat for the dairy industry
V8 – Phage M13
V9 – Phage display mechanism
V10 – Applications of M13
V11 – Applications of the CRISPR-Cas system

5. Glossary

The words in

Con forma

Con forma

Eliminado

Con forma

Con forma

Table 2 are used in the 'Bacterial Viruses in Biotechnology' framework and are explained in the context of this framework.

Eliminado

Table 2. Glossary

Word	Description
Aerosols	Suspension of liquid droplets in air
Algal blooms	Accumulation of algae in an aquatic system
Anterolateral thigh flap	A flap of skin and skin-related tissue of the lateral aspect of the anterior thigh
Antibiotics	Compounds that kill bacteria or slow down their growth
Antibodies	Proteins used by the immune system to recognize and bind to foreign material in order to remove them from the body
Antiseptic	Stopping or retarding the growth of microorganisms
Autoimmunity	Immune response of an organism against its own cells
Bacteremia	The presence of bacteria in the blood
Bacteria strains	A taxonomic rank in the classification of microorganisms, below the rank of species
Bactericidal	Killing bacteria
Bacteriologist	A person that professionally studies bacteriology (*i.e.* bacteria)
Base pairs	The building blocks of the DNA double helix structure that consist of two pairing bases: adenine (A) pairs with thymine (T) and guanine (G) with cytosine (C)
Bioassays	A method to characterize a compound (*e.g.* effective concentration) by adding it to living cells or tissue
Biocontrol	Methods to control infections based on biological processes
Biosphere	All ecosystems on the planet
Biotechnology	A technology based on biological systems (*e.g.* living organisms or parts) to develop products
Capsid	The protein shell of a virus
Carbon cycle	The flow of carbon atoms from the atmosphere to Earth and back
Cell wall	A structure surrounding cells
Chelating agents	Chemical compounds that are able to bind metal ions
Chromosome	Large DNA molecule that contains the genetic material of an organism
Clinical trials	Experiments that are performed in order to evaluate a certain drug in terms of safety and efficacy
Complementary sequence	A DNA sequence that can bind to a matching sequence via base pairing in order to form a double-stranded sequence
Crop rotation	Growing consecutively different crops on the same land
Debridement	Surgical technique that removes dead tissue in order to clean a wound
Decontamination	The removal of microorganisms
Disinfectants	Chemical compounds that inactivate or kill microorganisms
DNA ligase	An enzyme that joins the ends of two DNA strands
DNA polymerase	An enzyme involved in DNA replication: it adds bases to a DNA strand

DNA replication	A process that makes a copy of DNA based on the original DNA molecule, in order to amplify DNA
DNA sequencing	A process that determines the order of nucleotides in DNA. Multiple sequencing methods are available
Dysentery	Heavy, often bloody, diarrhea
Ecosystems	Natural systems composed of living organisms that interact with their environment
Eluted	To remove bound proteins from a matrix
Endonuclease	And enzyme that cuts within a DNA or RNA molecule
Enzymes	A protein that accelerate a chemical reaction
Fermentation	In the context of food processing: fermentation is the conversion of a substrate (*e.g.* sugar) via microorganisms in the presence of oxygen
Filamentous	A long thin cellular structure
Fistula	A tissue tunnel that develops between two hollow spaces
Flagella	Hair-like structure, used by cells to move
Food poisoning	An illness caused by eating food that is contaminated with infectious organisms
Genera	A taxonomic rank in the classification of microorganisms: a group of related species
Genes	DNA or RNA encoding a functional molecule
Genome editing	Techniques that modify the genome of an organism
Genomes	All the genetic material of an organism
GMOs	Genetically modified organisms: organisms with altered genetic material
Good Manufacturing Practice (GMP)	Guidelines recommended by authorities in order to manufacture and market products according to quality standards
Homologous recombination	In bacteria: a DNA repair process by exchanging genetic material between regions of two DNA strands with similar sequences
Hydroponically	Growing plants without soil, in a nutrient-containing aqueous solvent
Icosahedral	Geometrical shape with twenty triangular faces
Implant	Artificial object that is placed within the body
In situ	Locally, on site
In vitro	Outside a living organism, *e.g.* in a test tube
Intracellular parasitism	Phenomenon used to describe an organism that lives and reproduces in the cells of another organism
Knockouts of a gene	Modification of a gene in order to inhibit its functionality
Lysis	The dead of an organism by disruption of the cell membrane that surrounds the cell, resulting in the release of cellular components in the environment
Magistral preparations	Medicinal products that are prepared in a pharmacy by a pharmacist
Microbiologist	A person that professionally studies microorganisms
Microbiome	Microorganisms living in a specific environment and their genetic content
Microbiota	Microorganisms living in a specific environment
Molecular biology	The study of the structure, function and interaction of cellular molecules

Musculoskeletal	Related to both the muscular and skeletal system
Mutations	The alteration of a nucleotide in the DNA
Negative pressure wound therapy	A therapy in which negative pressure is applied on a wound to remove fluids. This therapy promotes the healing process. The wound is sealed with a bandage and a vacuum pump is applied
Non-homologous end-joining	DNA repair technique in which DNA ends that are non-homologous (no similar sequences) are joined
Nucleotide	Building block of DNA, consisting of a base (A, T, G or C) and a sugar- and phosphate group
Osteomyelitis	Infection in a bone
Pathogen	Microorganism that causes disease
Pathologist	A person that professionally studies pathogens
Peptides	Short chains of amino acids, which are the building blocks of proteins
Pesticides	Compounds that are used to destroy pests
Phage cocktails	A solution containing multiple and diverse phages with different host spectrum
Phage propagation	The amplification of phages by infection of a host cell
Phyllosphere	Parts of a plant that are above soil-level
Plasmids	Circular molecule carrying DNA, distinct from the chromosome
Polymeric	An organic compound that consists of consecutive repeats of similar molecules
Post-harvest	After harvesting
Preventive	In order to avoid an infection, a disease outbreak, *etc.*
Prokaryotic	Organisms that consist of one cell (*e.g.* bacteria)
Recombinant proteins	Proteins that are encoded by genes that have been modified
Recombination	Breaking DNA parts and recombining them in a different way
Reproduction	The production of new phage particles by infection of a host cell
Restriction enzymes	Enzymes that recognize a DNA sequence and subsequently cut the DNA at or near this sequence
Rhizogenic	Root-producing
Ribosomes	Complex of proteins and RNA involved in protein synthesis
RNA polymerase	Enzyme that accelerates the conversion of DNA to RNA
Sensory properties	Characteristics of food: texture, aroma, appearance and taste
Sepsis	Microorganisms in the blood or other tissue, leading to organ failure
Shelf-life	The time you can store a product
Species	Highest taxonomic rank in the classification of microorganisms: similar organisms within a genus
Symptomatic	Indications of a disease
Thermostability	Stable (*i.e.* no structural or functional changes) at high temperatures
Toxicity	Able to cause disease via toxins that damage tissue and disable the immune system
Transcription	Biological process to convert DNA to messenger RNA with the help of RNA polymerase

Transcription factors	Proteins that control certain parameters of the transcription process
Trauma patients	Patients with sudden physical injury (wound, broken bones, etc.)
UV irradiation	Electromagnetic radiation with wavelengths from 10-400 nm, present in sunlight
Virions	Virus particle
Whey	The liquid part of milk that remains after coagulation in cheese making