# FACTSHEET

ALTERNATIVES TO ANTIBIOTICS

## Introduction

Due to antibiotic resistance and the long-term lack of antibiotic discovery, alternative treatments and effective prevention strategies for bacterial infections are receiving increasing interest. Here, we briefly describe a few examples of such alternatives that currently are being researched, and we list some of their potential pros and cons (summarized in table 1). Most of the alternative treatment strategies included in this factsheet have been known for quite some time, but have for various reasons either not reached the market or have not had a real breakthrough on it. Thus, it is important to keep in mind that it is uncertain whether the alternatives that currently are in the drug-development pipeline (out of which we have just mentioned a few specific examples) eventually will be available on the market. A general drawback that applies for several of the alternative treatment strategies included in this factsheet is that their host range is too narrow to be able to outcompete antibiotics for the treatment of severe and life-threatening infections. All in all, this highlights the importance of optimizing the use of existing treatments and prevention strategies while at the same time developing useful, alternative treatments and diagnostic tools to address the problem with antibiotic resistance.

## Antibodies

The human immune system protects our bodies from intruding microorganisms, such as pathogenic bacteria and viruses. Antibodies are protein structures that are naturally produced by our immune system and function by specifically recognizing and neutralizing foreign organisms or molecules. Before antibiotics were discovered, infectious diseases were treated with "serum therapy" which in practice meant that antibodies were transferred from immune individuals to infected patients. Although the treatment was rather effective, it was at that time associated with toxic side effects. Now, industrially produced antibodies are considered an interesting and presumably safe future alternative to antibiotics and technical advances have made it possible to produce purified antibodies with low toxicity. However, the curative effect of antibodies decreases as the infection progresses, which means that they need to be administered as early as possible upon infection. In turn, this puts high demands on quick and effective diagnostics. Antibacterial antibodies will therefore best be used in combination with conventional antibiotics, or as prophylaxis. Thus, even if useful antibodies eventually will reach the market, the need for effective antibiotics will remain. Antibodies targeting *Clostridium difficile*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are in the drug-development pipeline.

## Probiotics

Probiotics contain live microorganisms that exert health benefits on the host upon consumption. The positive effects are obtained through restoration or maintenance of the host's normal flora, which averts colonization of pathogenic bacteria. Clinical trials of novel probiotics that specifically aim to treat or prevent diarrhea caused by *Clostridium* difficile are ongoing. Probiotics prevent or treat local infections, primarily of the gut, and cannot substitute antibiotics as a treatment of more severe bacterial infections.

## Vaccines

Prevention of infectious diseases through vaccination has been practiced for centuries. During vaccination, dead or attenuated bacteria or viruses are injected into the blood stream, which triggers the production of memory cells that produce antibodies. The antibodies will protect us from disease the next time these specific bacteria or viruses enter our bodies. Vaccination can lower the incidence of specific infectious diseases in a population, including infections with antibiotic resistant bacteria. Consequently, vaccination can aid in preserving effective antibiotics since a lower incidence of infections results in less need for antibiotic treatment, which in turn affects the resistance development of bacteria. There are currently many effective vaccines against both viral and bacterial diseases on the market, but there is still a problem with vaccine coverage, particularly in low- and middle-income countries. For example, despite the existence of an effective vaccine against the bacterium *Streptococcus pneumoniae*, it has been estimated that hundreds of thousands of children under the age of five die each year in infections caused by this bacterium. Global coverage of the *Streptococcus pneumoniae* vaccine would save many lives and would substantially reduce the need for antibiotic treatment in children. Novel vaccines against *Clostridium difficile* and *Staphylococcus aureus* are currently in the drug-development pipeline.

## Phage therapy

Phages, or bacteriophages, are viruses that infect bacteria. Phages are abundant in nature but can also be genetically engineered for selection of specific characteristics. The principle of phage therapy is that these very host-specific viruses are introduced during an active bacterial infection and selectively kill (alone or in combination with an antibiotic) the pathogenic bacteria. This treatment strategy has been applied in some countries, primarily in Eastern Europe during the 20$^{th}$ century, but is somewhat controversial in scientific and medical communities. There are several prerequisites for phage therapy. For example, the phages must be able to immediately kill the bacteria (be lytic) and their exact host range, biology and pharmacology needs to be determined before they can be used as therapeutics. Phages have low inherent toxicity but do partly consist of proteins, which may trigger a human immune response. The immune reactions could potentially result in elimination of the phages, but could also, depending on the intensity of the reaction, be harmful to patients. When phages are administered, they will multiply once they have infected their host

bacteria, which means that they will evolve in our bodies. A disadvantage of phage therapy is the potential of promoting emergence of phage-resistant bacterial pathogens. Since phages are very host specific, phage therapy will not affect the normal flora of humans, but will on the other hand not be a suitable treatment option for severe infections that need to be handled promptly before the pathogen is known. With the currently available diagnostic tools, it is too time-consuming and risky to determine the exact bacterial species before initiating treatment. A clinical trial evaluating the applicability of phage therapy for the treatment of *Pseudomonas aeruginosa*-induced burn infections is ongoing.

## Antimicrobial peptides

Antimicrobial peptides are parts of plants and animals' natural defense against various microorganisms, bacteria included. The peptides generally target and disrupt the bacterial cell membrane, which results in cell lysis and bacterial death. Antimicrobial peptides have a broad spectrum and could in theory be used against a variety of bacterial infections. The peptides have a rapid action and bacteria are potentially less prone to develop resistance against them, when compared to conventional antibiotics. On the other hand, they are instable and could potentially lose their antimicrobial properties quickly when entering our bodies. Also, antimicrobial peptides often exhibit cytotoxic effects on human cells and have therefore primarily been evaluated as topical treatments for local infections. An antimicrobial peptide product targeting *Pseudomonas aeruginosa* is in the drug-development pipeline.

| Alternatives to antibiotics | Pros | Cons | Comments |
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| **Antibodies** | Likely safe. Historically validated. | Expensive. Must be taken early upon onset of infection. | Narrow spectrum. For preventive and adjunctive use. |
| **Probiotics** | Help to establish or maintain the normal flora. | Only for local use. | A complement rather than an alternative. For preventive and therapeutic use. |
| **Vaccines** | May lower the incidence of bacterial infections and the need for antibiotics. Rather cost-effective and safe. | Species- or strain-specific. | For preventive use. |
| **Phage therapy** | Phages are abundant and easily isolated. May disrupt biofilms. | Could trigger harmful immune responses in humans. Risk for resistance | Narrow spectrum. For therapeutic and adjunctive use. |

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| | | development. | |
| **Antimicrobial peptides** | Rapid antibacterial effect. Broad spectrum activity. | Instable and cytotoxic. Only for topical use. | Broad spectrum. For therapeutic and adjunctive use. |

Table 1: Some anticipated pros and cons of a selected number of alternatives to antibiotics.

## Bibliography and suggested further reading

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