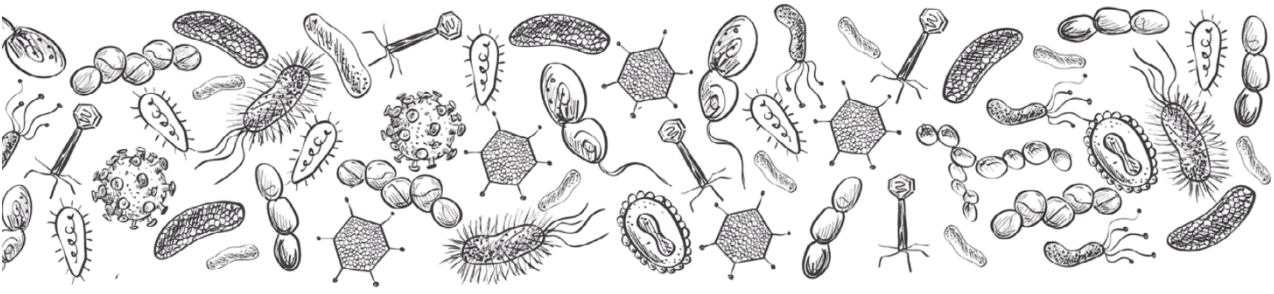
A clash of kings

Addendum

Impact



One of the major global health issues in the near future is the rise of antimicrobial resistance (AMR) caused by the widespread use of antibiotics. This 'silent' pandemic has not gained the attention that it should have. It already has a big impact on human health and on healthcare costs and will only do more so in the future. For example, In Europe 390,000 deaths annually are attributable to AMR and worldwide this counts up to 10 million by the year 2050 (O'Neill, 2016). Also economically AMR has a big impact: in Europe the healthcare costs and productivity losses are estimated to cost €1.5 billon each year (ECDC/EMEA, 2009). Furthermore, it is predicted by the World Bank that the economic damage caused by AMR in the next decades could result in a loss of world output between €2-6 trillion (World Bank, 2017).

Antibiotics have been the main treatment option for bacterial infections in humans for decades, and also have been used widely in veterinary medicine. Despite years of successfully treating these infections, it has at the same time also led to an increase of antimicrobial resistance genes (ARGs). Bacteria acquire these ARGs and humans become resistant against antibiotic therapy used. Especially bacteria that are resistant against multiple antibiotics pose a great risk for human health. Patients suffering from infections caused by these multi-drug resistant (MDR) bacteria bring substantial healthcare costs because of their prolonged hospital stays. And more importantly, the difficulty to treat these infections leads to a high mortality in patients suffering from infections with MDR bacteria. To combat these dangerous infections, alternative therapeutic options should be explored to complement antibiotics in the near future.

Next to the problems caused by MDR bacteria, antibiotics also have a disruptive effect on the human gut microbial communities. Antibiotics do not only kill or inhibit pathogenic bacteria, but also influence the commensal 'beneficial' microbes found in the gut, leading to dysbiosis. Dysbiosis subsequently affects human health as evidenced by the link between gut microbial dysbiosis and diseases such as inflammatory bowel disease, obesity and diabetes mellitus type II. These chronic conditions pose great health risks to a large part of the human population, and therefore the importance of a balanced gut microbiota should be considered. Not

only bacteria are influenced using antibiotics, but also fungi are affected. Fungi are also an important part of the gut microbial community, and the disruption of the bacterial community by antibiotics has shown to lead to outgrowth of (pathogenic) fungi. Infections caused by these fungi often have a high mortality and are difficult to treat. The increase of fungi after antibiotic use shows the importance of inter-kingdom relations in the human gut. Bacteria as well as fungi form a balanced community, and a disturbance of this community can have great influences on health. Future research should therefore not only focus on bacteria, but also fungi should be taken into account in microbial studies. In this thesis, tools have been explored to study fungi and bacterial-fungal interactions. Further development of these tools can help in understanding and solving problems caused by bacterial and fungal dysbiosis and will contribute to the understanding of their role in (human) health and disease, eventually contributing to prevention and/or therapy. Particularly the cross-kingdom interaction between the two will lead to novel insights and will likely improve medical practices in the future, with an expected reduction in associated healthcare costs.

The problems described above, show the urgent need for replacement of antibiotics as primary treatment options of bacterial infections. One promising alternative option, that is on the rise, is (bacterio)phage therapy, but it has been in the shadow of antibiotics for decades, therefore more research is needed for this to become a more standard clinical practice. In this thesis, tools have been investigated to help in the design of bacteriophage therapy. Good *in vitro* experiments are important to have a solid base for research on phage therapy, because of the specificity of bacteriophages to their bacterial host. Well-designed survival studies can increase the success rate of phage therapy, because it helps in determining the appropriate dosage and helps in exploring the need for protection techniques, such as encapsulation. This increase in success rate of phage therapy will decrease health-care costs due to the 'silent' pandemic caused by infections with AMR bacteria.

References

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