Viruses against bacteria

Bacteriophages – a unique opportunity in the fight against antibiotic resistance

Report from a cross-disciplinary work group

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“The threat of antibiotic resistance cannot be eliminated, but we must adopt measures to reduce the development of resistance and simultaneously organise ourselves to minimise the consequences for people and animals. This calls for a renewed commitment in several sectors.”
National Norwegian antibiotics strategy (2015–2020)

Introduction

Viruses against bacteria. Bacteriophages – a unique opportunity in the fight against antibiotic resistance

Norway's own prime minister and all the world's leaders face thousands of issues which must be dealt with and prioritised. Some are more pressing than others. One is antibiotic resistance. It must be at the top of the list, not only with Erna Solberg, the Norwegian prime minister, but also with government leaders worldwide.

We have no choice, and we're on overtime. Antibiotic resistance is a slow-moving pandemic which already threatens the health of people and animals worldwide. Although estimates are uncertain, antibiotic resistance could be causing as many as 33 000 deaths in Europe every year.[1] Modern medical treatments are in danger of becoming unusable. The threat of complications and longer spells in hospital is increasing. Welfare and the world economy are also threatened.

The World Bank on antimicrobial resistance

- **GDP:** Global GDP could fall by 1.1-3.8 per cent in 2050. Low-income countries will be hardest-hit, with a GDP reduction of up to five per cent.
- **Global poverty:** Growth in extreme poverty could increase by 28.3 million people, mostly in poor countries.
- **World trade:** Global exports could decline by 1.1-3.8 per cent in 2050.
- **Health costs:** Globally, health costs could increase by USD 300-1 000 per annum in 2050.
- **Livestock production:** Global livestock production could fall by 2.6-7.5 per cent in 2050.

Kilde: Verdensbanken[2]

Solberg was present when ACD Pharmaceuticals assembled some of Norway's leading specialists, academics and national authorities in the summer of 2020 to discuss how bacteriophages could become a sustainable and effective alternative to antibiotics for both people and animals, and how that could help to reduce threats to the environment, to curb the economic consequences of resistance, and to create new industry and jobs throughout Norway.

Erna Solberg challenged the work group to advise on how bacteriophages can be adopted as quickly as possible in the fight against antibiotic resistance, and how Norway can acquire a leading role here.

Photo: Raymond Skjerpeng

A year of the Covid-19 pandemic has demonstrated the dramatic consequences a health crisis can have for individuals, the economy and society. We must do what we can to ensure that this does not happen with a crisis we have warning of, like antibiotic resistance.

Solberg urged the participants to establish a work group which could advise on how bacteriophages can be deployed as rapidly as possible in the fight against antibiotic resistance, and on how Norway could acquire a leading role here.

This report is a response to the prime minister's challenge. The opportunities are many. Success is possible with the will and the right instruments.

The work group has been chaired by professor emeritus dr.med Lars Vorland. Hans Petter Kleppen, PhD, research director at ACD Pharmaceuticals AS, has served as secretary.


“Extensive use of antibiotics has led to challenges with resistance in a number of important sectors. In a world where everyone affects everyone else, antibiotic resistance must be resolved from a One Health perspective across sectors and national boundaries.”

The other members are:

- Anita Schumacher, *administrative director, University Hospital of North Norway (UNN)*
- Karita Bekkemellem, *managing director, Norwegian Association of Pharmaceutical Manufacturers (LMI)*
- Ingrid Stenstadvold Ross, general secretary, Norwegian Cancer Society
- Gaute Lenvik, *managing director, Norwegian Veterinary Institute*
- Anne Husebekk, *rector, UiT Arctic University of Norway*
- Gunnar Skov Simonsen, *professor, UiT and UNN*
- Jim-Roger Nordly, *CEO, Stim AS*

The Norwegian Medicines Agency has contributed to meetings and identified opportunities for contributing expertise and to the work of developing customised regulatory pathways for rapid adoption of the technology.

Antibiotic resistance threatens the environment, animals, food production and public health

“The threat of antibiotic resistance cannot be eliminated, but we must adopt measures to reduce the development of resistance and simultaneously organise ourselves to minimise the consequences for people and animals. This calls for a renewed commitment in several sectors.” National Norwegian antibiotics strategy (2015-2020)

Extensive use of antibiotics has led to challenges with resistance in a number of important sectors. In a world where everyone affects everyone else, antibiotic resistance must be resolved from a One Health perspective across sectors and national boundaries.

Global antibiotic consumption must be reduced, more and better vaccines must be developed, and new treatment options against harmful bacteria must be developed.[3]

Environmental consequences

Antibiotic resistance is the immediate consequence of overuse. But antibiotics also affect the environment and natural biological diversity.[4] More attention needs to be devoted to the consequences of antibiotic resistance for the environment and sustainability.[5]

Leakage of chemicals and antibiotics to the environment from antibiotic manufacture in such countries as India and China is so substantial that it destroys biological diversity, makes food production impossible and pollutes drinking water.[6] It creates breeding grounds for multiresistant bacteria which are transmitted to people and animals, with global consequences.

At the same time, using antibiotics for growth promotion contributes to an irresponsibly high level of consumption. As early as the 1940s, US studies showed that it was possible to halve production time for chickens by including low doses of antibiotics in their feed. Large quantities of these substances have been used with animals to improve feed utilisation, promote growth and yield a faster return. Utilising antibiotics as

growth promoters is forbidden in Norway, but contributes globally to irresponsibly high levels of antibiotic consumption in agriculture.[7] Indefensible quantities of antibiotics are also used preventively in large parts of the world to make healthy animals and harvests more resistant to illness.

All plants and animals are dependent on well-functioning microbiological communities in the environment. Using and releasing antibiotics can disrupt this microbiological diversity. More needs to be learnt about that as well.

Industry, environmental organisations and governments must work together, because the threat to the environment enhances the threat to public health, business and jobs.

Bacteriophages can replace antibiotics for applications in health and agriculture, and reduce emissions of the latter to the environment, cut the effect on the natural ecological balance and improve animal welfare.

Public health and modern medicine

Decades of medical research and progress could be set back as a result of antibiotic resistance. Hospital admissions could become longer, complications after medical interventions will increase and health care costs will rise dramatically.

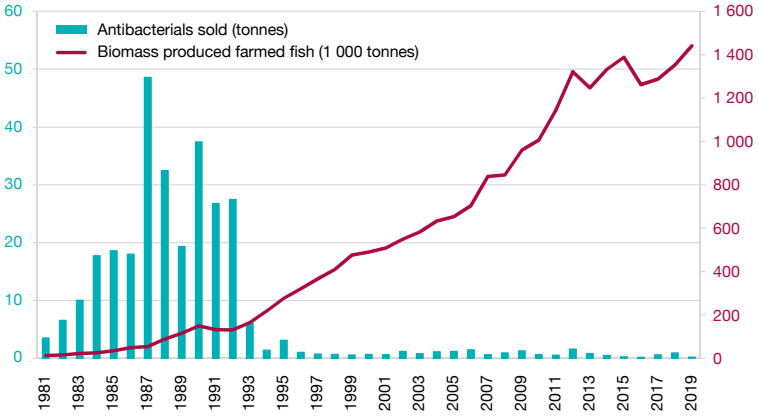
Without effective antibiotics to prevent or treat serious infections, many modern medical treatments would also be difficult to provide – including transplants, cancer treatment, dialysis and surgical interventions. The risk will be too great without antibiotics which work. That would turn the clock back and represent a serious threat to public health.

Almost 35 000 people in Norway develop cancer every year – 100 a day. Roughly 11 000 die of cancer annually. Globally, more than 18.2 million new cases occur and over 9.6 million cancer patients die every year.

Antibiotic-resistant bacteria will set cancer treatment back several decades. It will become more difficult and expensive, and more side and latent effects will be experienced. Many treatment opportunities will also disappear completely. This applies, for example, to patients with acute leukaemia and bone marrow cancer. That will increase mortality for cancer sufferers in the future.

Oslo University Hospital estimates that about 20 per cent of its patients receive antibiotics in connection with their cancer treatment. Source: Norwegian Cancer Society

European health authorities report that some 33 000 people already die annually in Europe because of antibiotic resistance[8] – in Norway alone, about 70 people died in 2018.[9]



Figur 1-1: *Sales, in tonnes of active substance, of veterinary antibacterials for treating farmed fish (including cleaner fish) in Norway from 1981 to 2019 compared with biomass produced (harvest weight). Reproduced from Norm/Norm-Vet 2019.[14]*

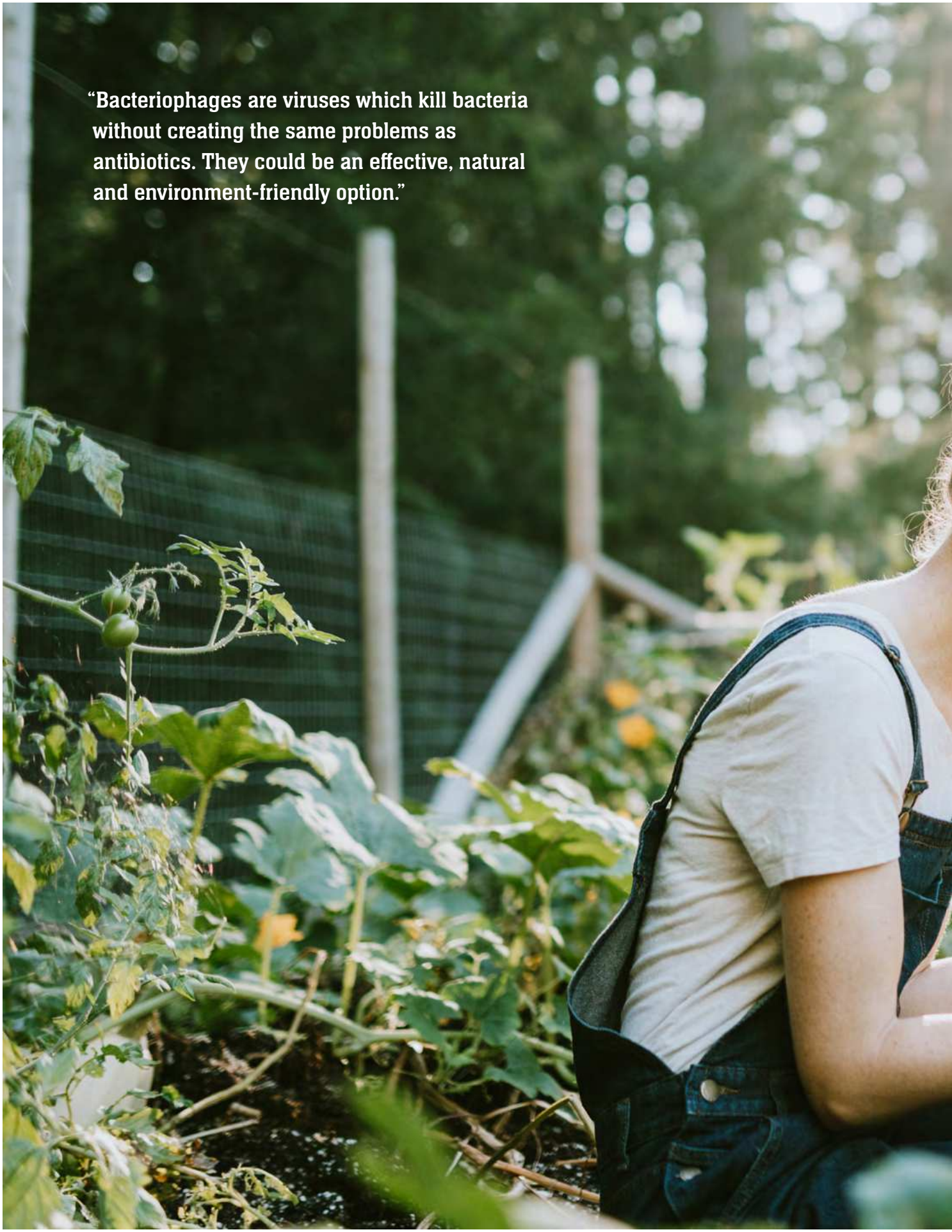
Antibiotic consumption in Norway

Norway is among the lowest users of antibiotics for both people and animals, and thereby has little antibiotic resistance today.

The use of antibiotics among Norwegians has declined by 33 per cent since 2012.[10] That is three percentage points above the government's goal of a 30 per cent reduction by 2020.[11] In other parts of the world, antibiotic consumption is high in all sectors and the resistance problem is large and growing. We see that healthy carriers of resistant bacteria and patients with infections from such organisms are also on the increase in Norway.[12] Norwegians travel and import food and other goods. The bacteria come along for the ride. Norway must be prepared for a growing domestic threat as well.

Norwegian agriculture and aquaculture also have a very low consumption of antibiotics, largely thanks to vaccination and good control of stock infection. However, this could change rapidly through imports of new bacteria which are difficult to control with vaccination and other measures. One example is the bacterium Piscirickettsia salmonis, the main reason why Chilean aquaculture uses about 1 000 times more antibiotics per kilogram of fish than Norwegian salmon farmers.[13]

During the 1980s and 1990s, consumption of antibiotics in Norwegian aquaculture was dangerously high – about 50 tonnes per 50 000 tonnes of fish in the latter decade. Systematic vaccination work reduced this amount significantly. See figure 1-1[14]). Norway currently produces some 1.3 million tonnes of farmed fish. Should antibiotics again become required, this would therefore be unsustainable. That would be unthinkable. It means that Norway's second largest industry could be devastated by a single bacterium if effective vaccines cannot be found fast enough. Developing such medications can be time-consuming, and sometimes ends in failure.


“Bacteriophages are viruses which kill bacteria without creating the same problems as antibiotics. They could be an effective, natural and environment-friendly option.”

Vaccination is an effective measure for reducing antibiotic consumption. Development and production of modern vaccines and bacteriophages build on the same biological knowledge and technology. So viewing these two processes together offers substantial opportunities for synergies in both development and production phases.

Norway needs other tools. The country must be prepared for incursions by bacteria which it lacks effective antibiotics and vaccines against. It must be in the forefront.

Bacteriophages – a sustainable and effective alternative to antibiotics

For more than three billion years, bacteriophages have specialised in infecting, killing and keeping bacteria under control. Some kill so effectively that they can be used purposefully instead of or in combination with antibiotics. Bacteriophages are viruses which kill bacteria without creating the same problems as antibiotics. They could be an effective, natural and environment-friendly option.

The effect of bacteriophages against bacteria was described by French-Canadian microbiologist Félix D'Herelle in the 1920s. Experiments were conducted in subsequent years on using bacteriophages against infections. Successful treatment with these viruses depends on knowing exactly which bacterial species are making the patient ill, so that the right bacteriophage can be deployed. This knowledge was not available in the 1920s and 1930s, and use of bacteriophages more or less ceased when Alexander Fleming discovered penicillin.

However, they continued to be used to treat infections in the Soviet Union and are still utilised today in such countries as Poland, Russia and Georgia when antibiotics prove ineffective against acne, sores, and skin, eye and gastrointestinal infections as well as against festering post-operative wounds in patients infected with antibiotic-resistant MRSA bacteria.[15]

Post-1945 research on bacteriophages laid the basis for developing molecular biology and modern gene technology. With modern diagnostic methods and increased knowledge of pathogenic bacteria, a renewed commitment is being made to developing bacteriophages as one solution to the growing threat of antibiotic resistance.

Good experience and many opportunities

Bacteriophages have applications in many areas, such as human and veterinary medicine, aquaculture, agriculture and food production.

A number of specific areas and problem bacteria are discussed below where bacteriophages have proved effective – and where they have a potential to play a prominent role against bacterial infections.

ACD Phamaceuticals was the first manufacturer in the world to introduce a bacteriophage product for aquaculture use. The Norwegian company launched this project in 2010 with the goal of developing bacteriophage-based solutions for bacterial challenges in the fish farming sector. That work resulted in a technology platform which can be used to develop bacteriophage products against harmful bacteria in both animals and people.

CUSTUS®$_{YRS}$ was introduced in 2018 as the world's first bacteriophage product for use in Norwegian aquaculture.

Although antibiotic consumption by Norway's fish farms is very low (figure 1-1), this industry represents a big challenge internationally – particularly in farming prawns and the freshwater fish tilapia. In cooperation with the University of Bergen and other partners internationally, ACD Pharma is developing bacteriophage solutions for both these areas.

Since 2019, ACD Pharma, the UiT, the UNN, Stavanger University Hospital, the Norwegian Veterinary Institute, the Karolinska Institute and a number of other international medical teams have been working together on the Kleb-Gap research project. This aims to utilise bacteriophages against *Klebsiella pneumoniae*, a bacterium which can cause pneumonia and hospital infections. Finding new defences against it has been identified as critical by the World Health Organisation (WHO).

Promising work is also under way to find bacteriophage products against methicillin-resistant *Staphylococcus aureus* (MRSA). This bacterium is commonly found among both people and animals, and can cross-infest between them. Some variants have developed resistance to several types of antibiotics. MRSA poses a serious threat to hospital patients and, if its presence increases, treatment of staphylococcus infections could become less effective and considerably more expensive.[16]

Infection by intestinal bacteria with the ESBL resistance mechanism has shown a dramatic rise internationally and is also increasing in Norway. Blood poisoning from MRSA and ESBL-carrying bacteria doubles the risk of death compared with comparable infections by antibiotic-sensitive bacteria.[17,18,19]

The WHO published a list in 2017 of the 12 bacterial families regarded as the biggest threat to public health globally because of their antibiotic resistance, and where alternative solutions urgently need to be found.

Findings have been published on bacteriophages with the potential for medical use against 10 of these 12. Developing bacteriophage-based solutions which could help to replace or reduce antibiotic consumption represents a big potential in the fight against antibiotic resistance.

One Health – collaboration across sectors and industries

The threat from antibiotic resistance can only be fought across sectors and industries from a One Health perspective, where an integrated approach is taken to the spread of resistance and alternative solutions. Progress and solutions in one sector must be highlighted and carried further in others.

"We want more collaboration between industry and the public sector. This also involves a requirement for industry to contribute expertise and to serve as a professional and orderly partner for Norway's public health service. If we are to be good at clinical studies in Norway, we must be partners, not competitors." Bent Høie, minister of health and care services. National action plan for clinical studies.[20]

Norwegian scientists and researchers in universities, hospitals and industry are already working together to identify more bacteriophages able to fight a steadily growing number of target bacteria in aquaculture, veterinary and human medicine. Similar collaboration must be extended and expanded in order for Norway to play a leading role in the field. The country must additionally build further on existing expertise through international collaboration. We believe that knowledge about bacteriophages also has to be included in basic education so that students learn more about them and see the opportunities they offer.

Norway must be even more open to collaboration with and learning from others – governments, health services, academia and industry. That is what the work group has done in this study. We represent different sectors and industries, but share a common goal of contributing to the fight against antibiotic resistance.

“Commercialisation calls for customisation and collaboration. Norway needs growth in new industries which can safeguard revenues as activities on and earnings from the Norwegian continental shelf gradually decrease. The health sector stands out as particularly interesting.”

Norway needs growth in new industries – health care is the future

Bacteriophages can help to resolve a health crisis while simultaneously contributing to new Norwegian jobs and industrial development.

Norway needs growth in new industries which can safeguard revenues as activities on and earnings from its continental shelf gradually decrease. The health sector stands out as particularly interesting. In its 2021 White Paper on long-term perspectives for the Norwegian economy, the government emphasises that the challenges faced must be met here and now. These have been reinforced by the Covid-19 pandemic. To overcome the challenges up to 2030 and 2060, the government will pursue policies which create growth in the private sector, increase employment and contribute to good use of resources in the public sector.

The health sector has the potential to become one of Norway's most vigorous and productive industries, and offers great development opportunities. In its White Paper on the health sector, entitled *Together for value creation and better services*, the government emphasised that this industry can contribute to growth and value creation in the Norwegian economy.[21] Already accounting for about three per cent of Norway's value creation, health care has grown by more than twice as much as the overall economy (excluding oil and gas) in recent years. The sector employed some 100 000 people in 2016, up by 18 per cent from 2008.

"By thinking innovatively, the sector can provide patients with good solutions while also securing new jobs. If companies are to succeed at this, however, provision must be made for closer collaboration between industry and the public health care system." Torbjørn Røe Isaksen, minister of trade and industry.[22]

The global market for innovation and commercialisation is substantial. That offers opportunities for future value creation. At the same time, it can provide benefits for both human and animal health and solutions to global environmental challenges.

Substantial sums are invested annually on research in Norway, and the government is the large source of such financing. In 2017, public sources accounted for almost 47 per cent of research funding.[23] The Research Council of Norway allocated about NOK 5.3 billion for R&D in 2019, including in the higher education sector, research institutes, health trusts and industry.[24] The last of these is the biggest sector pursuing R&D, with NOK 32.7 billion or 45 per cent of total investment in such activities during 2018.[25]

Norway must ensure that domestic public and private spending on expertise, research and innovation is commercialised to provide jobs and industrial development for the whole country.

Commercialisation calls for customisation and collaboration

Many opportunities are available. The Ministry of Health and Care Services is to draw up a new strategy for fighting antibiotic resistance. In its 2020 status report on knowledge gaps, challenges and relevant measures related to antibiotic resistance, the Norwegian Institute of Public Health noted that bacteriophages represent a new and exciting approach, but that commercialisation is a long way off.

We agree with that conclusion. However, this should be seen not as an obstacle but rather as an opportunity. As prime minister Erna Solberg put it so well:

"Our job is to facilitate that the good ideas round and about meet good and stable conditions which persuade entrepreneurs and industry to make a commitment".[26] *Prime minister Erna Solberg.*

Achieving rapid commercialisation is possible. Covid-19 has demonstrated that a vaccine can be developed, produced and registered in 10 months. That calls for financing and will – a joint commitment by government and industry.

Proposals

Norway can take a leading position. It has world-class scientific, research and innovation communities involved with human, fish and animal health, but needs pace-setters and more public-private collaboration. To get there, the country needs the following.

1. **Political action across sectors.** Good visions and intentions must be followed up by specific action. The responsible ministries have to do this in their own sectors – health and care services, climate and the environment, agriculture and food, and trade, industry and fisheries.

2. **More binding public-private collaboration.** A political expectation is that the big social challenges will be overcome in future through a close collaboration between public and private sectors. To succeed, this calls for clear commitments and

for detailing expectations on collaboration between public services, government and private players.

3. **More precisely targeted government support.** Incentives are needed which reduce risk and make commitments in Norway possible. The risk in both development and commercialisation phases is often too high for private players. Risk must therefore be shared between private enterprise and the government through such means as investment support for production and more research funding earmarked for antibiotic resistance. That can create industrial activity and jobs throughout Norway.

4. **Investment in infrastructure.** Investment is required in necessary infrastructure which can help convert innovations into jobs and industrial development in Norway, and which also makes the country a more attractive host for foreign research and industry.

5. **Clinical studies.** Making bacteriophages quickly available as a treatment option for humans calls for clinical studies which can contribute to the necessary documentation and knowledge. Clinical studies are a precondition for safe and efficient treatment methods. The national action plan provides a good basis for progress on putting bacteriophages in place for human use.

6. **Regulatory solutions.** Developing bacteriophages into an alternative to antibiotics calls for more effective and customised approval pathways. These must take account of the properties of such viruses and encourage their development and commercial use. The Norwegian Medicines Agency must be given the resources and responsibility to be able to play a leading regulatory role with bacteriophages, relating both to production and regulatory regimes internationally. If Norway is to manage to build up a health industry in this field, it must be a leader on the regulatory front.

7. **International commitment.** Antibiotic resistance is high on the global health agenda. Norway has spoken with a clear voice on this issue over time in the WHO, the EU and Nordic collaboration. The country has taken a position on vaccines, in part through the global Gavi vaccine alliance and the Coalition for Epidemic Preparedness Innovations (Cepi).[27,28] A Norwegian commitment to and commercialisation of bacteriophage products provides a unique opportunity for Norway to contribute not only with engagement and funding, but also with specific solutions in the fight against antibiotic resistance.

In our work on this report, we have brought together representatives for patients, academia, the health service, government agencies and industry. Jointly, we have identified challenges and opportunities. A very good and highly interesting collaboration has demonstrated that all the participants see opportunities in the technology. We have identified the strength and potential offered by working together across sectors and industries. We can learn from each other. Other players in Norway have both an interest in and expertise on this subject: patients, aquaculture, environmental and agricultural organisations, other research communities, private industry and government agencies. We invite them all to a continued collaboration.

We wish to thank prime minister Solberg for taking the initiative on producing this report and for thereby placing an important issue on the agenda. We hope that her engagement with antibiotic resistance and bacteriophages will be further encouraged after reading the report.

Norway is the best in the world on antibiotic resistance and the use of vaccines. Within aquaculture, it is also the best at developing and producing vaccines. Innovations and knowledge from one sector must be transferred to overcome challenges in others.

The country could now become the best for bacteriophages. The opportunity is there.

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professor emeritus dr. med.

Gunnar Skov Simonsen
professor, UiT and UNN

Ingrid Stenstadvold Ross
general secretary, Norwegian Cancer Society

Gaute Lenvik
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About the work group

Lars Vorland

Professor emeritus dr.med, health leader and former managing director, Northern Norway Regional Health Authority

Vorland is a Grand Old Man in the Norwegian health service and a specialist in medical microbiology. As managing director of the Northern Norway RHA, he chaired the National System for Managed Introduction of New Health Technologies in the Specialist Health Service for four years. This system determines which methods and medicines can be used in the specialist health service.

Photo: Northern Norway RHA

Ingrid Stenstadvold Ross

General secretary, Norwegian Cancer Society

Stenstadvold Ross has been general secretary of the Cancer Society since March 2020, and has worked at the society for seven years – most recently as manager of the communication and society department. She was earlier with the Norwegian Association for the Hearing Impaired and the National Association for Public Health. She is chair of the Dam Foundation, a board member of the Association of Norwegian Knowledge-based Enterprises, and a member of the council of HealthCare21.

Gunnar Skov Simonsen

Professor, department for medical biology, UiT Arctic University of Norway in Tromsø, and head, department of microbiology and infection control, University Hospital of North Norway (UNN)

Simonsen is also responsible for the Norwegian Surveillance System for Antimicrobial Drug Resistance (Norm) at the UNN. He holds a part-time post as senior consultant at the Norwegian Institute of Public Health and has led work on a new knowledge gap report for the Ministry of Health and Care Services in connection with a new national antibiotic strategy.

Anne Husebekk

Rector UiT Arctic University of Norway

Husebekk has been rector of the UiT since 2013. She is professor dr.med in immunology at the department of medical biology, and a specialist in immunology and transfusion medicine.

Photo: Skjalg Bøhmer Vold

Gaute Lenvik

Managing director, Norwegian Veterinary Institute

Lenvik was previously managing director for food and agriculture and food and bio at the Confederation of Norwegian Enterprise (NHO). Before that, he served as assistant director and acting director general at the Ministry of Agriculture and Food with responsibility for research, innovation and regional policy. The Veterinary Institute is a research and emergency response body owned by the Ministry of Agriculture and Food. It devotes equal attention to fish and animal health, and works with the whole chain from animal health and welfare to feed and food security.

Anita Schumacher

Administrative director, University Hospital of North Norway (UNN)

Schumacher has been administrative director of the UNN since January 2019. She served previously as specialist director, clinic manager and department head at Vestfold Hospital, medical division director at Akershus University Hospital and director of strategic expertise development at the Southern and Eastern Norway Regional Health Authority. Schumacher studied medicine, specialising in internal medicine and then infection medicine.

Karita Bekkemellem

Managing director, Norwegian Association of Pharmaceutical Manufacturers (LMI)

Bekkemellem is a former politician who served five terms as a member of the Storting (parliament) for Møre og Romsdal (1989-90), and was a minister in two governments. She has been managing director of the LMI since 2009.

Jim-Roger Nordly

CEO, Stim AS

Nordly has built up several successful companies supplying the aquaculture sector in Norway and internationally. They produce and deliver products and services related to pharmacy, fish health, environmental monitoring, biosecurity and nutrition. Nordly speaks with a clear voice on issues relating to the aquaculture sector's opportunities, challenges and operating parameters.

Hans Petter Kleppen

Research director at Stim AS and ACD Pharmaceuticals AS

Kleppen studied molecular biology at the University of Bergen and took his PhD at the Norwegian University of Life Sciences (NMBU) on the interaction between bacteria and bacteriophages in industrial fermentation. He has led R&D work on bacteriophages at ACD Pharma and Stim since 2010.

Technical report on bacteriophages in the fight against antibiotic resistance

Contents

Antibiotic resistance – a major threat – bacteriophages an answer

Antibiotic resistance is already claiming lives. Although Norway is in a very advantageous position, conditions globally are a matter of grave concern. Bacteriophages could be an effective, natural and environment-friendly tool against antibiotic resistance in both people and animals. This technical part of the report describes the requirements for and presents a set of recommendations on how Norway can take a leading role in helping to ensure that bacteriophages contribute to the fight against antibiotic resistance. This will prevent the use of antibiotics and develop new treatment options against resistant bacteria.

Requirements

Requirement 1:
Quality assurance of biological production
Preconditions for adopting bacteriophages in medical and other applications are that:

- only suitable bacteriophages and host bacteria are used
- bacteriophages are produced only from quality-assured seed stocks
- a quality system is used in production which ensures that unwanted bacteriophages, genes or genetic products do not contaminate the products

Requirement 2:
Resistance strategy
- When marketing a product with active (live) bacteriophages, it must be possible to present an effective resistance strategy for the product and its use.

Requirement 3:
Correspondence between target bacteria and bacteriophages used
- A correspondence must exist between the target bacteria to be combated and the bacteriophages used.
- Those who are going to market a bacteriophage-based product to fight a particular target bacteria must document in advance that the bacteriophages used are effective against the (dominant) type of bacterial species they are to be deployed against. This is done by mapping the diversity of the target bacteria as part of product development and/or for each patient group ahead of treatment with the bacteriophages.

Requirement 4:
Knowledge of where and how the target bacterium occurs
- Effective use of bacteriophages in fighting specific bacteria calls for detailed understanding of where and how the target bacteria occur. The administration method and dosage must be customised so that the bacteriophages are delivered with the correct density for coming into contact with the target bacteria.

Requirement 5:
Sensible use of bacteriophages
- The use of bacteriophages in food production and animal husbandry must not replace other infection hygiene measures.


“Global antibiotic consumption must be reduced, more and better vaccines must be developed, and new treatment options against harmful bacteria must be developed.”

Recommendations

Recommendation 1:
Bacteriophages to reduce the carrier status of antibiotic-resistant bacteria with healthy carriers

We believe that suitable R&D projects must be pursued to permit the use of bacteriophages against the asymptomatic carrier status of harmful bacteria.

Examples of target bacteria suitable for R&D commitments include extended spectrum beta-lactamase (ESBL) *E coli*, ESBL *Klebsiella pneumoniae* in people, and MRSA in pigs and people.

Recommendation 2:
Bacteriophages for use in ensuring food security

We believe that R&D projects must be pursued with the aim of establishing regulatory approval pathways for non-medical use of bacteriophages.

An example of a target bacterium suitable for this R&D commitment is *Listeria monocytogenes*

Recommendation 3:
Bacteriophages for medical treatment

We believe that approval pathways for medical use of bacteriophages must be established, and that this should be done in parallel with and in close association with R&D projects aimed at developing specific bacteriophage-based medicines. This will ensure correspondence between the regulations and bacteriophage biology while ensuring that quality requirements for product and documentation are met.

Recommendation 4:
Bacteriophages against biofilms

We recommend that R&D projects are pursued with the aim of developing bacteriophage-based products and solutions against biofilms. These involve the use of biofilm-penetrating bacteriophages and biofilm-degrading enzymes derived from bacteriophages. These projects should be conducted with bacteria and bacteriophages of great medical and economic significance. Examples include *Staphylococcus aureus, Pseudomonas aeruginosa*, ESBL *E coli*, *Listeria monocytogenes* and *Flavobacterium psychrophilum*.

Furthermore, we recommend that a basic research project be conducted to identify the molecular mechanisms in the interaction between bacteriophages and host bacteria which govern the latter's "decision" on whether to form a biofilm. Knowledge about this would permit the development of preventive bacteriophage products which can hinder biofilm formation.

Recommendation 5:
Increased expertise about and establishment of regulatory practice on non-medical use

We recommend that the Norwegian Food Safety Authority strengthens its expertise with bacteriophages and establishes a practice for approving bacteriophage-based products in non-medical areas of application. This can be achieved by creating a specialist group on bacteriophages which establishes, in cooperation with relevant specialists and also possibly with the Norwegian Scientific Committee for Food and the Environment (VKM), routines for evaluating and approving the quality and safety of bacteriophage-based products. Potentially dangerous applications of bacteriophages can thereby be excluded.

Recommendation 6:
Establishing an effective approval system for medical use

No country currently has effective systems to approve bacteriophages for medical use. The Norwegian Medicines Agency already has the necessary expertise with these viruses and the capabilities required to develop a regime which allows them to be adopted quickly for treating bacterial illnesses in people. It is also envisaged that such a regime could provide a model for other national and international health authorities.

We recommend that the Ministry of Health and Care Services asks the Norwegian Medicines Agency to study the opportunities offered by current regulations and possibly to identify new and effective approval regimes which make provision for adopting bacteriophages as an effective alternative to antibiotics.

Recommendation 7:
Establishing a cross-disciplinary group to evaluate and develop regulatory solutions

We recommend the appointment of a cross-disciplinary group with expertise in human and veterinary medical microbiology, bacteriophage biology and business development, as well as regulatory/legal expertise on documenting the quality, safety and efficacy of medicines, in order to support the planning and execution of the R&D projects recommended in this report. Such an arrangement will make it possible to evaluate and develop regulatory solutions at a detailed level while the projects are under way.

"Further R&D is required in order to utilise the full potential of bacteriophages in the fight against antibiotic resistance."

Bacteriophages – nature's biocontrol mechanism

Bacteriophages are viruses which have specialised over billions of years in infecting, killing and keeping bacteria under control. They are found everywhere, in our bodies, in the food we eat and, on every leaf, and blade of grass on Earth. Bacteriophages represent the most numerous lifeform on the planet, and a vast range of variants can be found.

Viruses are simple organisms which lack the ability to reproduce themselves. They need a host cell to multiply.

Bacteriophages function in nature as an effective biological control system, scaling back bacteria which have become too dominant in an environment. That ensures the great microbiological diversity which every ecosystem on the planet depends on, from the oceans to human intestines. Since bacteriophages have developed and specialised in parallel with their host bacteria, all bacterial species have their own dedicated viral assailants, and each of these can only attack quite specific target bacteria.

Because of their narrow specificity, bacteriophages can be used for targeted removal of specific bacteria without affecting the remaining healthy microflora. That also avoids the diarrhoea and other common side-effects of antibiotics caused by dysbiosis – destruction of the normal intestinal microflora. However, a narrow host specificity also means that the bacteria to be eliminated must be known so that the correct bacteriophages can be deployed.

Choosing the right bacteriophages

A vast variety of bacteriophages exist. Some types are better suited than others for medical and other active use. Knowing which of them are suitable for what application is important.

Fundamentally different types of viruses can be found among the enormous diversity of bacteriophages. All known forms of genetic material (DNA and RNA, built up from one or two strands) are represented, and an unknown number of morphological variants exist for each of these.[29] Figure 2-1 presents an overview of some bacteriophage families which represent part of this diversity.

Caudovirales order – best suited for medical and other purposes

About 95 per cent of all bacteriophages which have been isolated and described belong to the *Caudovirales* order. This is the best known and described type of bacteriophage, and the best understood.[30] It is thereby also the one normally used for medical and other purposes. This is the classic bacteriophage with "head and tail".

Its genetic material comprises double-stranded DNA (dsDNA), protected by a protein coat with a tail-like attachment (illustrated in figure 2-1). The "tail" is a hollow tube which functions like a syringe needle when the bacteriophage injects its genetic material into the host bacterium. Receptor-binding structures at the tip of the tail recognise and bind the bacteriophage to the specific host bacterium. Recognition and binding between bacteriophage and the receptors on the host bacterium activate the "syringe" so that the former's genetic material is injected into the latter and takes it over.

The *Caudovirales* order contains a very diverse array of bacteriophages, with different methods of reproduction (life strategies). This also affects how they can be used purposefully against bacteria and infections.

Only purely lytic bacteriophages are suitable for medical and other use

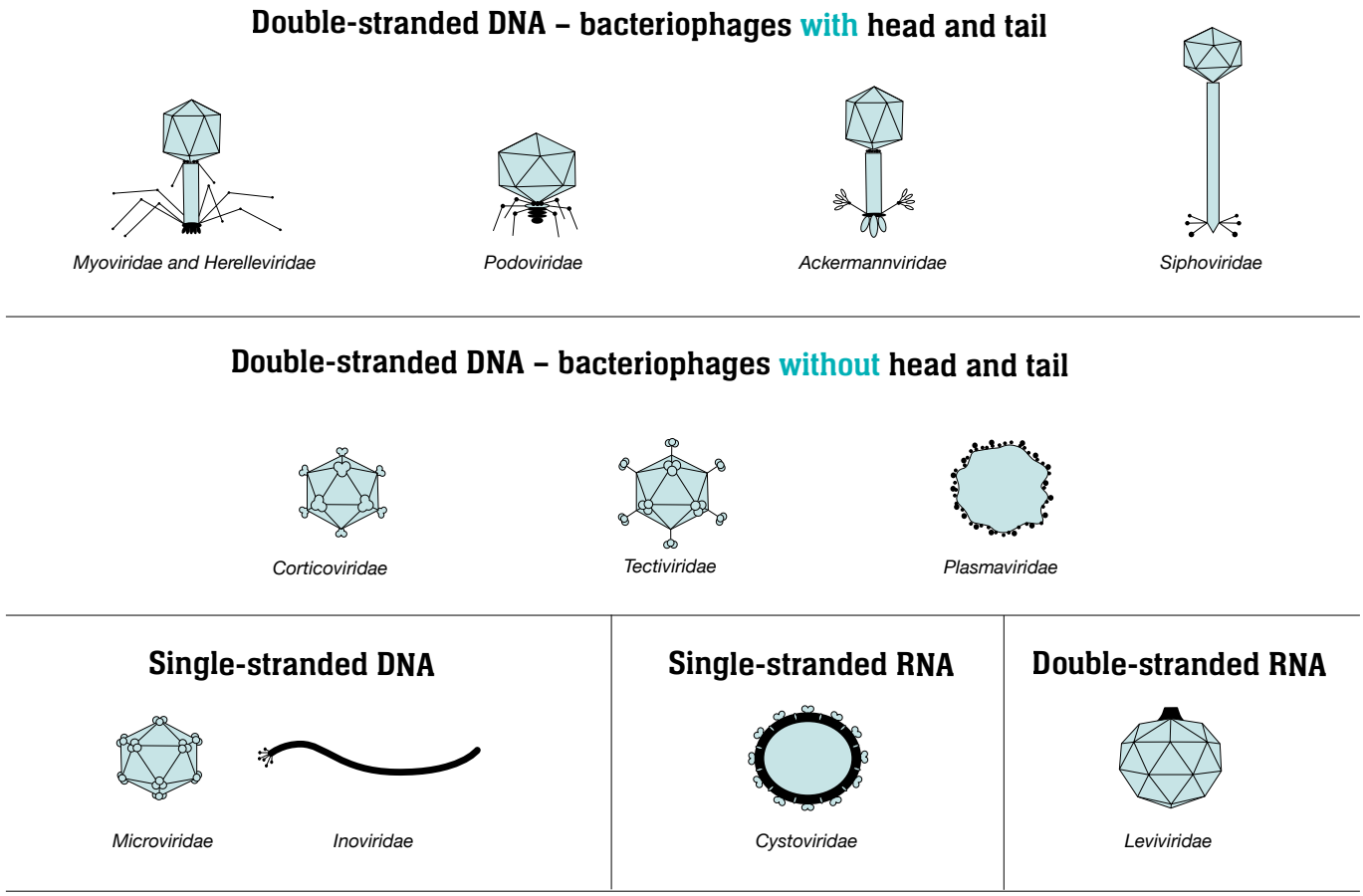
All *Caudovirales* are able to pursue a lytic life cycle. This is a precondition for both medical and other use. Such a cycle for a bacteriophage ends with the host bacterium destroyed and no longer able to grow and cause damage (figure 2-2 A). So only purely lytic bacteriophages are suitable for production and active use.

However, some *Caudovirales* bacteriophages can also reproduce through a lysogenic life cycle (figure 2.2 B). Their use can lead to bacteriophage resistance and undesirable gene transfer between bacteria. These *Caudovirales* bacteriophages are therefore unsuitable for either medical or other use.

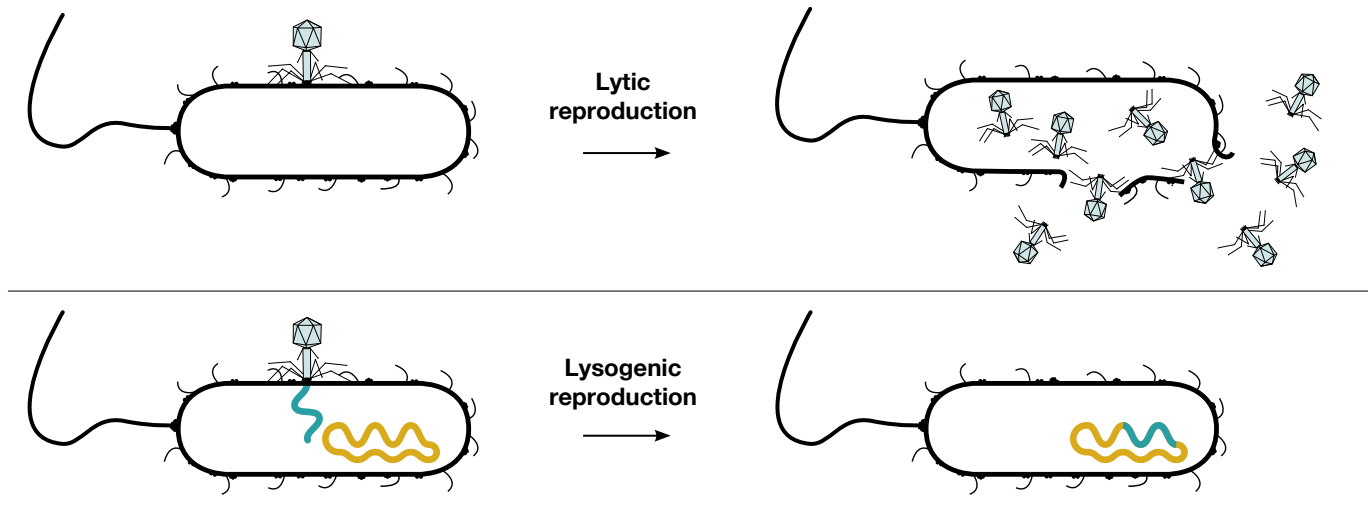
As a result, host bacteria to be used in producing bacteriophages must be quality-checked to ensure that lysogenic bacteriophages or undesirable genes from these do not enter the product.

Bacteriophages which reproduce lytically – suitable for medical and other use

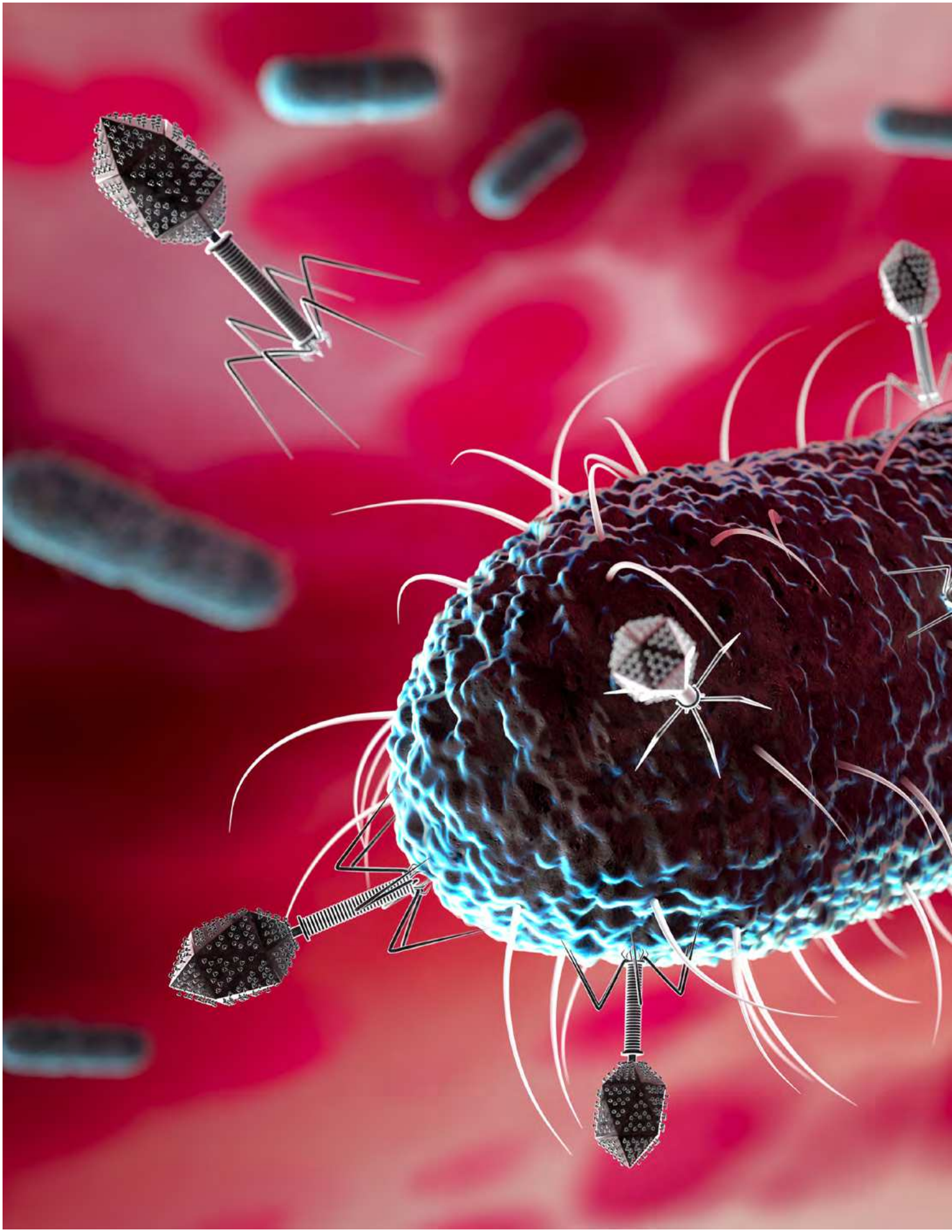
Lytic reproduction begins with specific recognition of and binding to a host bacterium. The bacteriophage then injects its genetic material into the host and takes it over. Physiological activity in the host is used to produce new bacteriophage particles. Finally, the bacterium is destroyed and releases new bacteriophages into the environment to seek further hosts to infect.



Figur 2-1: *Overview of a selection of bacteriophage families which illustrates a little of the huge diversity of these viruses. The Caudovirales order, which comprises the "head-tail" type, accounts for about 95 per cent of bacteriophages which have been scientifically described.*



Figur 2-2: *Different bacteriophages can reproduce in different ways after infecting a suitable host bacterium. Two common but fundamentally different reproductive strategies are illustrated here. Lytic reproduction (A) ends with the host bacterium bursting (undergoing lysis) to release newly formed bacteriophage particles. Lysogenic bacteriophages (B) can also reproduce by integrating their genetic material (red) in the host bacterium's DNA, and thereby reproducing as part of the bacterium when the latter divides.*



“A vast variety of bacteriophages exist. Some types are better suited than others for medical and other active use.”

Lysogenic bacteriophages – harmful and unsuitable for use

In addition to lytic reproduction, some bacteriophages can pursue a lysogenic lifestyle. They incorporate their genetic material temporarily into the host bacterium's DNA, and can then reproduce as part of the latter when it divides. Lysogenic bacteriophages increase their own reproductiveness by enhancing the ability of the host bacteria to reproduce. They therefore often carry genes which help the host to spread more readily. These genes can have harmful consequences, such as virulence, toxicity or antibiotic resistance. Lysogenic bacteriophages can thereby alter the host bacteria and make them more dangerous. An example is that they can carry genes which convert benign *E. coli* into a dangerous form.[31]

Requirement 1: Quality assurance of biological production

Preconditions for adopting bacteriophages in medical and other applications are that:

- *only suitable bacteriophages and host bacteria are used*
- *bacteriophages are produced only from quality-assured seed stocks*
- *a quality system is used in production which ensures that unwanted bacteriophages, genes or genetic products do not contaminate the products.*

Three-billion-year arms race

Bacteria can develop resistance to bacteriophages and do so as soon as they get the opportunity. These resistance mechanisms can take a number of forms.[32] They can prevent the bacteriophage recognising them, block its ability to bind to the bacterium's surface, or halt an infection process.

The bacteriophages have developed countermoves against the various resistance mechanisms, and a constant "arms race" has been waged between bacteria and bacteriophages since the first bacteria emerged about three billion years ago.

Good resistance strategies tilts the race in favour of the bacteriophages

Effective use of bacteriophages calls for good strategies to prevent the target bacteria developing resistance. These will tilt the race in favour of the bacteriophages. It is usually possible to establish an effective resistance strategy when using bacteriophages. That makes these viruses very suitable for use without resistance developing.

Factors which must be taken into account when developing a good resistance strategy are listed below.

1. **«Survival of the fittest»:** Resistance to a bacteriophage costs the bacterium functionality and competitiveness. It is possible to select bacteriophages which cost the bacteria a lot to defend against. Resistant bacteria will then be outcompeted by the rest of the microflora.

2. **Cocktails:** It is very unlikely that a bacteria will become resistant to two different bacteriophages simultaneously. Several different bacteriophages should therefore be used against the same target bacterium, either simultaneously (cocktail) or in series.

3. **Short time – high concentration:** Using a high concentration of bacteriophages for short periods, with gaps between treatments, reduces the danger of persistent resistance.

4. **Application area:** A conscious approach must be taken to where possible resistant bacteria end up, so that they do not pose a threat of reduced effectiveness for later treatment with the same bacteriophages.

5. **Avoid harmful physiological changes:** Documentation must be provided that the bacteriophages used do not encourage harmful physiological chances in the target bacteria. An example is Pseudomonas aeruginosa infections in patients with cystic fibrosis, where certain types of bacteriophages can encourage the bacteria to form biofilms to protect against the viruses. This can increase the harmful effect of the bacteria.[33]

In cases where it is nevertheless difficult to establish an effective resistance strategy, the target bacteria may be unsuitable for active use of bacteriophages, or genetically modified viruses may have to be utilised.

Requirement 2: Resistance strategy

- *When marketing a product with active (live) bacteriophages, it must be possible to present an effective resistance strategy for the product and its use.*

Specialised bacteriophages require knowledge of the target bacteria

Bacteriophages have narrow host spectrums. They are very specialised and can only infect and kill specific bacteria. Each bacteriophage has its quite specific target bacteria, which are usually confined to species, subspecies or strain levels. What bacteria are causing a disease must therefore be known in order to identify which bacteriophages can be used with the desired effect.

Treatment of individual patients or outbreaks requires sufficient time to determine which bacteriophages each patient requires, and that these are available for use when required.

Modern diagnostic methods make this possible. With some bacteria, however, their diversity must first be established so that the diagnostic tools can be customised to determine which bacteriophages will be effective.

Bacteriophage products intended to have a broad-spectrum effect, so that detailed diagnosis is not required ahead of treatment, must be composed of a large number of different viruses to be effective against the variety of target bacteria to be fought.

CUSTUS®YRS

Although CUSTUS®YRS comprises just two bacteriophages, it nevertheless covers the diversity of the *Yersinia ruckeri* target bacterium found in Norwegian salmon farms.

But the product is not effective against Norwegian variants of *Y. ruckeri* which attack rainbow trout. Geographical customisation will also probably be necessary if it is to be used in other salmon markets such as Chile or Scotland.

Requirement 3: Correspondence between target bacteria and bacteriophages used

- *A correspondence must exist between the target bacteria to be combated and the bacteriophages used.*
- *Those who are going to market a bacteriophage-based product to fight a particular target bacteria must document in advance that the bacteriophages used are effective against the (dominant) type of bacterial species they are to be deployed against. This is done by mapping the diversity of the target bacteria as part of product development and/or for each patient group ahead of treatment with the bacteriophages.*

Immune response to bacteriophages

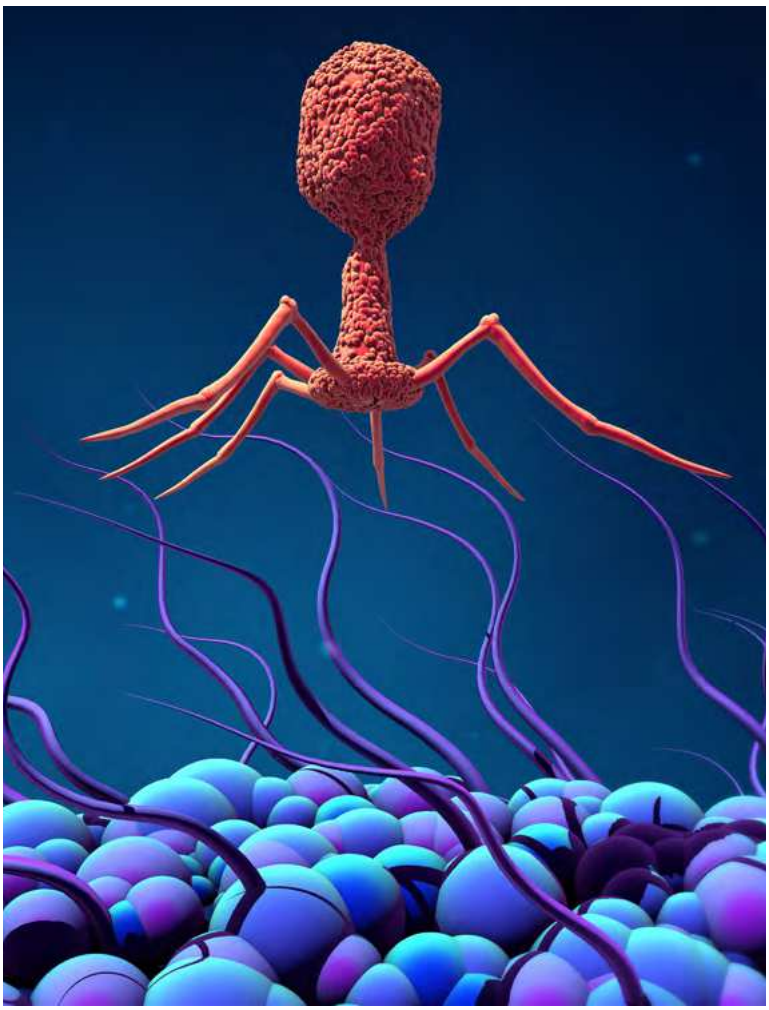
Both people and animals can develop an immune response to bacteriophages.[34] Such immunity may mean that repeated use of the same bacteriophage with a patient will eventually make the treatment less effective.

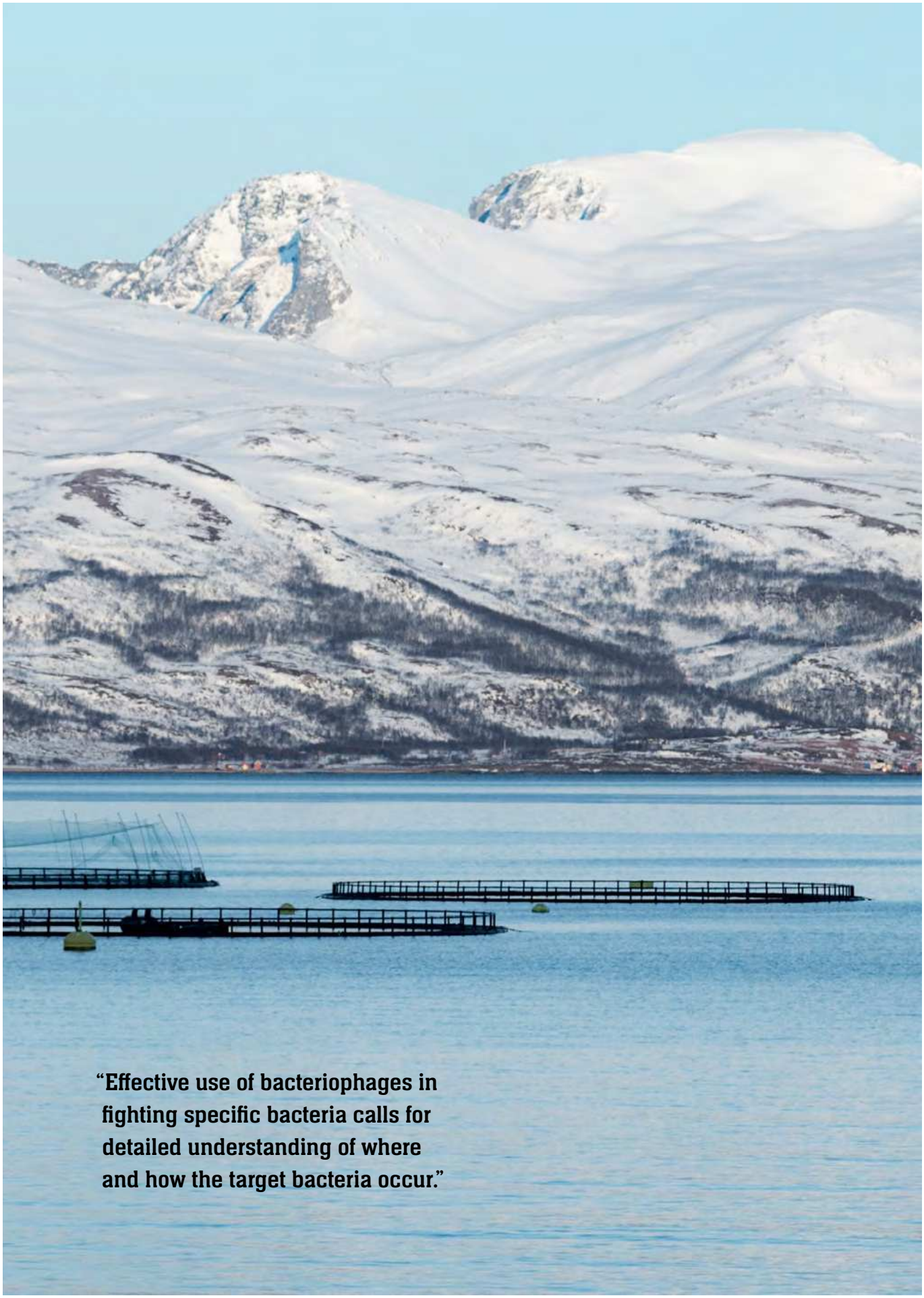
When bacteriophages are injected or used in such a way that they become exposed to the patient's immune system, the therapist must be conscious that an immune response is possible when selecting bacteriophages, determining the dosage and designing the treatment regime. It is also possible to breed or genetically modify bacteriophages to stimulate the immune system less.

Bacteriophages are safe to use and can be administered without side-effects

Safety in use is one of the main advantages of bacteriophages. Generally speaking, good documentation has been provided that these viruses are safe and can be administered without side effects to people and animals. This has also been shown for cancer patients and others with weakened immune systems.[35]

Only less serious side effects have been reported, such as allergic reactions and certain cases of endotoxin poisoning derived from the bacteria used to produce the bacteriophages and incomplete cleaning of the bacteriophage product. Good quality systems are therefore crucial in bacteriophage production to avoid or reduce possible side effects.





“Effective use of bacteriophages in fighting specific bacteria calls for detailed understanding of where and how the target bacteria occur.”

Safety must be documented in accordance with the quality standards which apply to the relevant area of application for each bacteriophage product.

Bacteriophage production
Bacteriophages are produced by cultivating a high density of relevant host bacteria under optimal conditions in a bioreactor before infecting them with the virus to be produced. When the bacteriophages have completed their infection and the hosts are destroyed, bacterial residues and growth medium are washed away. The end product is a solution of cleaned bacteriophages. The degree of cleaning is determined by the quality standards set for the application where the bacteriophages are to be used. Requirements for preparations injected in the patient, for example, are stricter than for those administered orally.

How are bacteriophages used? Basic principles
Where and when do the target bacteria become enriched?
Bacteriophages are at their most effective when the target bacteria are actively reproducing and multiplying. But they can also be used to defeat existing infections.

To achieve the desired effect, dosages and use must be tailored to the way the bacteria occur at the intervention point. That includes determining whether they are actively reproducing or in a dormant state, whether their density is high or low, and whether they are forming biofilms.

The intervention point can be in a patient or animal group exposed to ongoing infection, in healthy carriers of harmful bacteria, or an external source of infection in the environment.

Using bacteriophages in an effective manner requires knowledge about how the target bacteria is transmitted between patients and/or between different infection sources. When this is known, bacteriophages can be used for:

1. preventive biocontrol, which prevents the target bacterium from spreading in infection sources in the environment
2. preventive (prophylactic) medical treatment
3. antibacterial treatment of existing illness.

The administration method and dosing must be customised to ensure that the density of bacteriophages supplied is sufficient for them to come into contact with the target bacteria at the intervention point.

A prevailing view has been that, since bacteriophages can reproduce during use, a low dosage can be utilised. Research shows that the dosage and administration method can seldom be based on such *in situ* reproduction. Predicting the effect of this reproduction is very difficult, especially in those cases where the concentration of host bacteria is low.

Requirement 4: Knowledge of where and how the target bacterium occurs
Effective use of bacteriophages in fighting specific bacteria calls for detailed understanding of where and how the target bacteria occur. The administration method and dosage must be customised so that the bacteriophages are delivered with the correct density for coming into contact with the target bacteria.

Bacteriophages have a number of areas of application with both people and animals
The term “bacteriophage” is wide-ranging – probably as wide-ranging as the term “plant” – and these viruses therefore have a great many areas of application, from construction materials in nanotechnology, via tools and model systems in molecular biology and gene technology, to diagnostics, vaccines and tools for seeking new medicines.

“Live” bacteriophages can be used for various antibacterial applications in human and veterinary medicine, aquaculture, agriculture and food production. It is important to note that the use of bacteriophages for antibacterial purposes must not replace other infection hygiene measures.

In addition to the areas of application mentioned above, a number have been discovered by accident when bacteriophages give an effect which nobody was aware off. They play a role, for example, in maturing cheese and wine, in biofilters for water treatment, and in faecal transplants (injection of intestinal flora from a healthy donor) for treating chronic intestinal infections among humans.

Requirement 5: Sensible use of bacteriophages
The use of bacteriophages in food production and animal husbandry must not replace other infection hygiene measures.

Biofilms
A promising area for applying bacteriophages is combating biofilms.

These are formed by bacteria as a defensive mechanism against environmental factors, antibacterial agents and the body’s immune system. They comprise bacterial communities surrounded by a self-generated matrix of proteins and polysaccharides. Bacteria encapsulated

in a biofilm are difficult to eliminate by conventional antibacterial strategies, such as antibiotics.

Current research at the Norwegian Veterinary Institute shows that antibiotic treatment of bacteria in a biofilm not only fails to kill the bacteria but also increases the risk of developing antibiotic resistance. Such bacteria have displayed up to 4 000 times greater tolerance to antibiotics than when they are free-living. Biofilm formation has also been found to increase gene exchange between bacteria, including the transmission of ESBL and other antibiotic-resistance mechanisms.[36]

In addition to protecting the bacteria, biofilm is directly significant for the progress of most chronic infections, is the most important cause of persistent non-healing sores, and is involved in the development of several forms of cancer. See table 2-1 below.[37,38]

Body system	Organs	Illness
Hearing	Middle ear	Middle ear infection (Otitis media)
Circulation	Heart	Infectious endocarditis
	Arteries	Arteriosclerosis
Digestion	Salivary glands	Salivary gland stones
	Gallbladder	Chronic typhoid fever and predisposition to pancreatic cancer
	Intestines (large and small)	Chronic inflammatory bowel disease and bowel cancer
Connective tissue	Cutaneous and subcutaneous tissue	Sores
Reproduction	Vagina	Bacterial vaginosis (vaginitis)
	Womb and Fallopian tubes	Chronic endometriosis
	Mammary glands	Mastitis
Airways	Nose and sinuses	Chronic sinusitis
	Throat, tonsils and vocal chords	Sore throat, tonsillitis and infections of the vocal chords
	Upper and lower respiratory tract	Whooping cough and other Bordetella infections
	Upper and lower respiratory tract	Cystic fibrosis
Urinary tract	Prostate gland	Prostatitis
	Kidneys, bladder and ureter	Urinary tract infections

Table 2-1: *Overview of biofilm-related illnesses (Vestby et al, 2020).*

US calculations suggest that biofilm-related infections affect about 17 million Americans, cause 550 000 deaths and cost the US health service several billion dollars every year.[39,40,41]

Bacteriophages can be used to combat bacteria in a biofilm in the following ways:

- Several types of bacteriophages have enzymes on their surface which actively break down biofilms.
- Bacteriophages can penetrate the biofilm and attack "dormant" bacteria (persister cells), which are particularly resistant to antibiotics, for example.
- Bacteriophages have been shown to inhibit biofilm formation by bacteria. Very promising results have been reported, for example, from the use of bacteriophages to prevent biofilm formation by Flavobacterium psychrophilum, a bacterium which causes very great considerable in the aquaculture sector.[42,43]

Gene technology – genetically modified bacteriophages

Bacteriophages are relatively simple organisms. They have therefore been used by scientists to study fundamental biological principles. Early research on bacteriophages laid the basis for developing modern molecular biology and gene technology. Their simple biology and suitability for genetic manipulation mean that a number of companies and scientific teams around the world are seeking to develop genetically modified bacteriophages for various purposes.

Summary of requirements for using bacteriophages

We believe that bacteriophages have a very considerable potential in the fight against antibiotic resistance as an alternative to antibiotics, and not least in eliminating the need for antibiotics.

Bacteriophages have many areas of application across sectors. They can be used for people and animals in line with the One Health principle.

Since bacteriophage biology and mode of operation differ from those of other antimicrobial agents, it is important that bacteriophage-based antimicrobial solutions are developed and applied in accordance with the necessary requirements.

1. Only appropriate lytic bacteriophages can be used, and they must be produced in accordance with a quality system which ensures that products are not contaminated by unwanted bacteriophages, genes or genetic products.
2. To prevent resistance, bacteriophages must only be used in accordance with an effective resistance strategy.
3. Document must be provided that bacteriophage products comprise types which are effective against the variety of target bacteria it is claimed to deal with, and a plan must exist for updating the product if the diversity of target bacteria change – through imported infection, for instance.
4. Use of bacteriophages must be based on thorough advance knowledge of the target bacterium’s nature. Effective use of bacteriophages depends on an adequate number of them coming into contact with the target bacteria when and where the latter are to be combated.
5. Use of bacteriophages in food products and livestock must not replace the use of other infection hygiene measures.

“With modern diagnostic methods and increased knowledge of pathogenic bacteria, a renewed commitment is being made to developing bacteriophages as one solution to the growing threat of antibiotic resistance.”

Priority target bacteria in the fight against antibiotic resistance

A number of possible target bacteria and areas of application exist where bacteriophages could be effective in the fight against antibiotic resistance.

This chapter presents priority target bacteria and provides examples of R&D projects which could contribute to establishing various approval regimes for bacteriophage-based products, and thereby open the way for the commercial commitment needed if bacteriophages are to become a genuine solution in the fight against antibiotic resistance.

The choice of target bacteria and areas of application for bacteriophages against human pathogenic bacteria is based on the WHO's list of priority pathogens and on the monitoring and reporting of antibiotic resistance from Norm/Norm-Vet, the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (Efsa) and the European Medicines Agency (EMA). An evaluation has also been made of which target bacteria should be prioritised in animal husbandry, aquaculture and food safety.

WHO's priority pathogens
Ranking of pathogens in the WHO's priority list is based on the following criteria:

1. Mortality
2. Health and social burden
3. Prevalence of resistance
4. Trend in resistance development for past 10 years
5. Transfer of resistance
6. Available preventive measures in hospitals and society
7. Alternative treatments
8. Status for developing effective new antibiotics.

The list includes pathogens which cause illness in people, but a number of the target bacteria are also relevant for veterinary medicine and food safety. It includes bacteria which threaten public health globally. Regional differences will exist in the priorities, and bacteria not on the list could have a high priority in certain geographical areas.

Findings have been published on bacteriophages with the potential for medicinal use against 10 of these 12. Developing bacteriophage-based solutions which could help to replace or reduce antibiotic consumption represents a big potential in the fight against antibiotic resistance.

Priority		Bacterial species	Resistance
Critical	1	*Acinetobacter baumannii*	carbapenem
	2	*Pseudomonas aeruginosa*	carbapenem
	3	***Enterobacteriaceae***	carbapenem, 3rd gen cephalosporin (ESBL)
		Klebsiella pneumoniae	
		Escherichia coli	
		Enterobacter spp	
		Serratia spp	
		Proteus spp	
		Providencia spp	
		Morganella spp	
High	4	*Enterococcus faecium*	vancomycin
	5	*Staphylococcus aureus*	methicillin, vancomycin
	6	*Helicobacter pylori*	clarithromycin
	7	*Campylobacter*	fluoroquinolone
	8	*Salmonella spp*	fluoroquinolone
	9	*Neisseria gonorrhoeae*	3rd gen cephalosporin, fluoroquinolone
Medium	10	*Streptococcus pneumoniae*	penicillin
	11	*Haemophilus influenzae*	ampicillin
	12	*Shigella spp*	fluoroquinolone

Table 2-2 *WHO's priority pathogens.*[44]

Other priority target bacteria in animal husbandry, aquaculture and food safety

The incidence of serious bacterial illnesses in Norway is generally low in animal husbandry, aquaculture and food. This reflects a cool climate and systematic work on biosecurity and hygiene to avoid the transmission of infection and ensure the lowest possible use of antibiotics.

Internationally, the position is very different. Extensive use of 27 different classes of antibiotics is reported globally in animal husbandry and aquaculture. That makes a strong contribution to the development of resistance in these sectors, and a significant danger that antibiotic resistance will spread to people.[45] Norway must also be prepared for the threat represented by the global position.

Table 2-3 presents an overview of target bacteria which cause serious illness in Norway and the EU, and where priority must be given to finding new defensive solutions. This overview is not complete, but represents a selection of important target bacteria within the work group's areas of competence.

	Bacterial species	Resistance	Area
1	Listeria monocytogenes	Unknown	Food safety
2	Staphylococcus aureus (MRSA)	methicillin, vancomycin	Animal husbandry, zoonoses
3	Campylobacter jejuni	ciprofloxacin	Animal husbandry, zoonoses
4	Salmonella sp	ciprofloxacin + +	Animal husbandry, zoonoses
5	Escherichia coli	ciprofloxacin + +	Animal husbandry, zoonoses
7	Moritella viscosa	Unknown	Aquaculture
8	Flavobacterium psychrophilum	Unknown	Aquaculture
9	Tenacibaculum spp.	Unknown	Aquaculture
10	Pasteurella spp	Unknown	Aquaculture
11	Patogene Vibrio spp	Unknown	Aquaculture
12	Staphylococcus pseudointermedius	methicillin + +	Dogs, zoonoses
13	Streptococcus agalactiae	Unknown	Aquaculture
14	Piscirickettsia salmonis	Unknown	Aquaculture

Table 2-3: *Overview of important pathogenic bacteria affecting animal husbandry, aquaculture and food safety. The target bacteria are not listed in order of priority.*

Priority areas for R&D projects with bacteriophages

Human medicine

Where human medicine is concerned, prevention of carrier status and treatment of chronic infection are probably the easiest and most relevant areas of application for bacteriophages. Where carrier status is known, prevention of post-operative infections could also be relevant areas of application.

More research will be needed to establish effective treatments for illnesses which require a rapid response. Choosing the correct bacteriophages for medical treatment calls for sophisticated diagnosis, which is currently time-consuming. However, more effective methods are constantly being developed. Several international companies and research teams are working to develop rapid diagnostic test based on the detection of protein-protein interactions between various infectious agents and bacteriophages (phage display). Such technology will make it possible to utilise bacteriophages for treating subacute infections which currently account for a substantial proportion of antibiotic prescriptions.

Livestock, aquaculture and food production

Fewer challenges are presented by a lack of early diagnosis for illnesses and zoonotic bacteria in animal husbandry, land-based aquaculture and food security because livestock farming and food production are subject to stringent biosafety measures. Few new agents intrude, while "house strains" of bacteria persist in the facilities over many years and production cycles. That makes it possible to predict which target bacteria will be encountered and thereby to be ready in advance with the right bacteriophages.

Work group recommendation on R&D commitments

We recommend the following priority R&D commitments to establish regulatory pathways and contribute to a faster breakthrough in various areas of application for bacteriophages, at the same time as specific products and solutions are developed for use in the fight against antibiotic resistance. The projects we identify are suitable for industrial development and commercialisation. They will also open the way for developing bacteriophage-based products aimed at other target bacteria in similar areas of application.

1. **Bacteriophages to reduce carrier status of antibiotic-resistant bacteria in healthy carriers.** Examples of target bacteria suitable for R&D commitments are extended spectrum beta-lactamase (ESBL) *E. coli,* ESBL *Klebsiella pneumoniae* in people og MRSA in pigs and people.

2. **Bacteriophages to ensure food safety.** An example of a target bacteria suitable for an R&D commitment is *Listeria monocytogenes.*

3. **Bacteriophages for medical treatment.** R&D commitments should cover infections which are currently difficult to treat with antibiotics, as well as illnesses involving overuse of antibiotics internationally.

4. **Bacteriophages against biofilms.**
   a. Development of biofilm-penetrating bacteriophage-based products and solutions.
   b. Basic research project aimed at clarifying how certain bacteriophages initiate or prevent biofilm formation by bacteria. This could provide the basis for developing new biofilm-blocking medications.

The sections below provide a general description of how bacteriophage products are developed through research, and examples of specific R&D projects.

Which R&D projects are to be implemented in each priority area must be determined by the players planning them. Targeted public-private collaborations will be needed, where experience and expertise from academic, research teams, government agencies and the health service work together from a One Health perspective.

Collective assessments can be made of specific projects and solutions which meet requirements in different sector, while also creating industrial development in Norway.

R&D requirements, expertise and modes of collaboration

Further R&D is required in order to utilise the full potential of bacteriophages in the fight against antibiotic resistance. In order for bacteriophages to be adopted for medical use, a great need exists for good clinical studies and efficacy documentation conducted to western medical standards.

It has so far proved very difficult to produce efficacy documentation for bacteriophages which comply with today's guidelines for such studies.[46] For more details, see the chapter below on regulatory solutions. This means that the development of bacteriophages for medical use has been at a standstill over the past 10-15 years. Official regulators have awaited data from clinical studies, while companies developing bacteriophages have responded that it is impossible to deliver the information requested because these virus do not "fit the mould".

This position can be resolved through close collaboration between scientists, industry and regulators. Designs and models must be developed for conducting clinical studies which take account both of bacteriophage biology and quality requirements for documentation.

The development projects we recommend have been chosen because they are readily implementable within a reasonable time frame, are medically and economically important, and are suitable for establishing regulatory pathways for bacteriophage-based products.

Development of bacteriophage-based products
New bacteriophage-based products are developed in accordance with a set of work packages as shown in figure 2-3.

Different development projects will pass through the same work packages regardless of whether the target product is intended for fish, terrestrial animals or people, or whether it is defined as biocontrol or medicine.

Regulatory definition and area of application have great significance for the scope of work, time and cost in the various work packages, since different quality requirements are specified for production and for documentation of safety and efficacy. It is also simpler to recruit test animals for field studies than patients for clinical trials in people. In addition, the diversity and complexity of the target bacteria will affect project scope.

More detailed description of the priority areas

Recommendation 1: Bacteriophages to reduce the carrier status of antibiotic-resistant bacteria with healthy carriers.
We believe that suitable R&D projects must be pursued to permit the use of bacteriophages against the asymptomatic carrier status of harmful bacteria.

Examples of target bacteria suitable for R&D commitments include extended spectrum beta-lactamase (ESBL) E coli, *ESBL* Klebsiella pneumoniae *in people, and MRSA in pigs and people.*

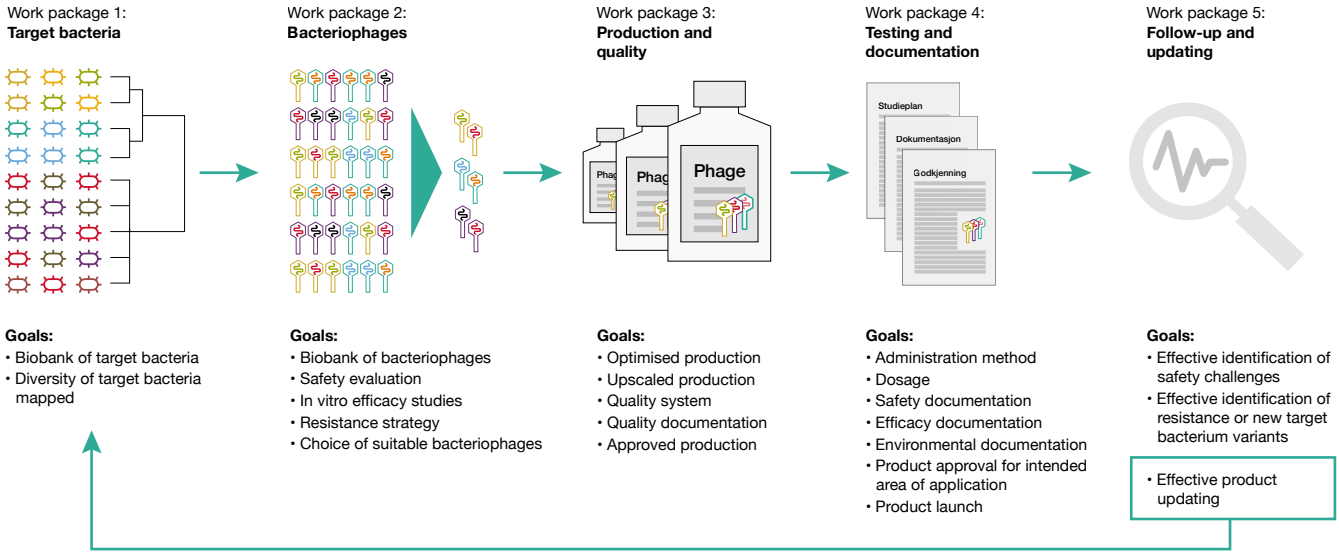


Figure 2-3: Overview of overarching R&D content in development projects for bacteriophage-based products.

Bacteriophages to reduce carrier status of ESBL Escherichia coli

E. coli is the bacterium targeted by the largest quantity of prescribed antibiotics in both Norway and the rest of the world. That has led to a sharp rise in its level of resistance among people in Norway and globally. ESBL-producing E. coli are a particular cause for concern. Since ESBL is an enzyme which breaks down certain kinds of antibiotics, bacteria which produce it are thereby resistant. The incidence of ESBL in clinical isolates has increased over the past 10-15 years from less than one per cent to five-six per cent in Norway. A steady increase of about 0.5 per cent annually is seen globally.

Resistance in *E. coli* is driven by a limited number of clones in people. This is promising, because it indicates that the diversity of the target bacteria can be overcome by a manageable number of bacteriophages.

E. coli is a common intestinal bacterium in most terrestrial animals, and pathogenic variants can cause illness in a great many species. People are usually infected through food, contact with infection in the environment, or direct contact with animals or people carrying pathogenic variants of the bacterium.

A growing proportion of the world's population are healthy carriers of ESBL *E. coli,* which has been described as a looming global pandemi.[47] A review of 62 scientific publications covering 29 872 healthy people observed an eight-fold increase in healthy carriers of ESBL *E. coli* over the past 20 years. The highest carrier status was found in south-east Asia (27 per cent) and the lowest in Europe (six per cent).[48]

Bacteriophages are being used against pathogenic *E. coli* for food safety (pre-slaughter washing of cattle in the USA) and have been used in two clinical trials with people for treating diarrhoea in Bangladesh and for infections with burns.[49,50] The two clinical studies yielded excellent safety documentation but inconclusive efficacy data because of an excessive diversity of target bacteria (insufficient screening when enrolling patients) in the first case and quality challenges with the test product used in the other.

Biocontrol or preventive treatment of healthy carriers among both people and animals, as well as use in food safety to prevent the transmission of specific sequence types, will be important areas of application for bacteriophages against ESBL *E. coli*.

Bacteriophages to reduce carrier status of ESBL Klebsiella pneumoniae

The level of resistance in Klebsiella pneumoniae is also rising among people in Norway and globally. Resistance to carbapenems as a result of increasing incidences of ESBL is a matter of serious concern. While the problem in Europe is greatest in the Mediterranean countries, it is also rising in the Nordic region. Sixty to 70 cases are identified in Norway every year. These are largely imported infections at the moment, but ESBL K. pneumoniae is also set to become endemic in Norway.

Infection with this bacterium occurs primarily in hospital and among people who are healthy carriers. These people pose a risk of spreading resistance in hospitals and are more exposed to serious post-operative complications than others.

The varieties of *K. pneumoniae* are dominated by a few sequence types, with ST307 as the most prominent and expansive.


“It is important to emphasise that bacteriophage products to be used for food safety are not an alternative to good food hygiene, but a supplement which will provide additional security against dangerous infectious agents in food.”

Bacteriophages against (ESBL) *K. pneumoniae* can be used to control infection pressure in healthy carriers ahead of hospital admission and for treatment of chronic infections.

The ongoing Kleb-Gap research project headed by the UiT is studying the use of bacteriophages against ESBL *K. pneumoniae.*

Promising work is also under way to find bacteriophage products against MRSA or *Staphylococcus aureus*. This bacterium is common among people and animals, and cross-infects between them. Certain *S. aureus* bacteria have developed resistance against several types of antibiotics. Infection with methicillin-resistant *S. aureus* (MRSA) is a serious threat to hospital patients. Should the incidence of MRSA in hospitals increase, treating staphylococcal infections could become less effective and significantly more expensive.[51]

We believe that R&D projects must be implemented which can open the way to the use of bacteriophages against the asymptomatic carrier status of dangerous bacteria. The target products would be used ahead of hospital admission to reduce the risk of infection transmission in the hospital and to the patient. Bacteriophage products developed to reduce infection transmission of ESBL *E. coli*, ESBL *K. pneumoniae* and MRSA are examples of this.

Norwegian medical teams, industry and regulators have the expertise required to implement such projects.

Recommendation 2: Bacteriophages for use in ensuring food security.
We believe that R&D projects must be pursued with the aim of establishing regulatory approval pathways for non-medical use of bacteriophages.

An example of a target bacterium suitable for this R&D commitment is Listeria monocytogenes.

Bacteriophages to ensure food safety in relation to Listeria monocytogenes

Listeriosis affects both animals and people. It is caused by the *Listeria monocytogenes* bacterium, widely distributed in nature and most animal species. Food is the commonest infection source for people.

This illness can affect all warm-blooded animals, leading to encephalitis and abortion. Sheep and cattle fed on silage are particularly vulnerable. The bacterium can reproduce in food at refrigerator temperature.

Most people occasionally consume food containing *Listeria* bacteria without becoming sick, but people with a weakened immune system may develop a serious illness. Old age, immunosuppressive treatment, pregnancy, alcoholism or underlying illnesses such as cancer or diabetes are examples of conditions which predispose to listeriosis. The bacterium may be transferred in the womb from mother to foetus, and can cause life-threatening illnesses in the latter.

In 2017, 2 500 cases of listeriosis were reported in the EU and the European Economic Area (EEA). Iceland, Finland and Denmark had the largest number of cases per 100 f000 people. *L. monocytogenes* may be found in hard-to-clean areas in food processing plants. The bacterium forms biofilms, which complicates taking hygiene measures against it. Each processing plant typically has its own "house strain".

Strict controls are applied for the concentration and incidence of *Listeria* in food and its production. The bacterium can grow even at refrigerator temperatures. Norway has had a number of listeriosis outbreaks from raw fish. Several bacteriophage products against *Listeria* are available in other countries. These are used in food processing (fresh and smoked fish, dairy products, fresh finished products) and on processing equipment to prevent *Listeria* growth.

Such products are used under a generally recognised as safe (Gras – see chapter 6) declaration in the USA. The EU has been considering the approval of Listex-P100 for more than a decade, but its use is permitted in certain member states.

The American product ListShield™ has been tested against Norwegian *Listeria* strains, but has not demonstrated sufficiently broad coverage of these to be effective in Norway.

Whether bacteriophage products available on the market are suitable for Norway's *Listeria* diversity must be investigated if they are to be effective in the country. New products containing bacteriophages customised to the Norwegian range will probably need to be developed.

It is important to emphasise that bacteriophage products to be used for food safety are not an alternative to good food hygiene, but a supplement which will provide additional security against dangerous infectious agents in food.

We believe that R&D projects must be pursued which lead to the establishment of regulatory approval pathways for non-medical use of bacteriophages. Developing bacteriophage-based products against *Listeria* to be used for food safety in raw fish processing and for biocontrol in producing silage feed for sheep and cattle are examples of suitable R&D projects.

Norwegian scientists, industry and regulators have the expertise required to implement such projects. Nofima, the Norwegian Veterinary Institute, the NMBU and ACD Pharma, for example, have previously conducted various research projects with Listeria and bacteriophages.

Recommendation 3: Bacteriophages for medical treatment

We believe that approval pathways for medical use of bacteriophages must be established, and that this should be done in parallel with and in close association with R&D projects aimed at developing specific bacteriophage-based medicines. This will ensure correspondence between the regulations and bacteriophage biology while ensuring that quality requirements for product and documentation are met.

The R&D projects should cover priority infections which are currently difficult to treat with antibiotics, as well as illnesses involving overuse of antibiotics internationally.

Medical treatment

As discussed in the paragraphs on regulatory approval regimes for bacteriophages, establishing approval pathways for medical use of these viruses is important. This should be done in parallel with and in association with the conduct of R&D projects. That would ensure correspondence between the regulations and bacteriophage biology, while also satisfying western medical quality requirements for production and clinical documentation.

As discussed in the paragraphs above, a large number of illnesses are to be found nationally and internationally which could be suitable for the development of bacteriophage-based medicines and appropriate approval regimes for medical use. Both public and private players are already at work on a number of these. Which R&D projects are most suitable as pilots for developing approval regimes must be determined in close collaboration between veterinary and human medical specialists, industry and regulators.

Recommendation 4: Bacteriophages against biofilms

We recommend that R&D projects are pursued with the aim of developing bacteriophage-based products and solutions against biofilms. These involve the use of biofilm-penetrating bacteriophages and biofilm-degrading enzymes derived from bacteriophages. These projects should be conducted with bacteria and bacteriophages of great medical and economic significance. Examples include Staphylococcus aureus*,* Pseudomonas aeruginosa*, ESBL* E coli*,* Listeria monocytogenes *and* Flavobacterium psychrophilum.

Furthermore, we recommend that a basic research project be conducted to identify the molecular mechanisms in the interaction between bacteriophages and host bacteria which govern the latter's "decision" on whether to form a biofilm. Knowledge about this would permit the development of preventive bacteriophage products which can hinder biofilm formation.

Biofilm

Combating biofilm represents a promising area of application for bacteriophages. In addition to being able to kill bacteria in biofilm directly, bacteriophages include several types with surface enzymes which actively break down such films. Bacteriophages also exist which can inhibit biofilm formation through other mechanisms.

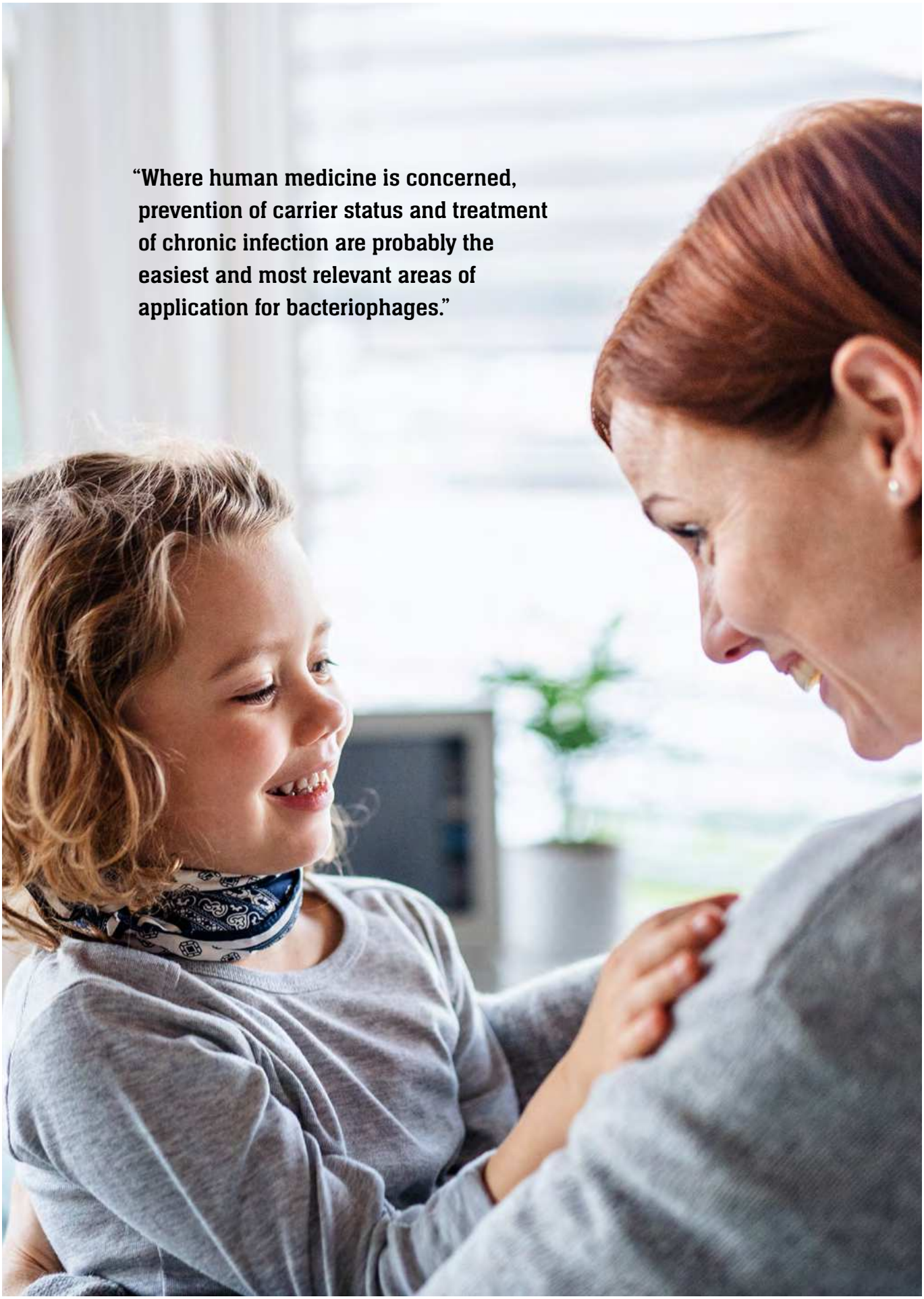
The vast majority of harmful bacteria, and probably all, are capable of forming biofilm. This increases their resistance to antimicrobial measures, such as antibiotics, and their ability to transmit infection. Biofilm formation is also an important virulence factor for many bacteria, and an important factor for the development of illness in most chronic infections.

Developing products which can kill bacteria in biofilms may provide important alternatives for treating chronic infections, where antibiotics do not work but, on the contrary, increase the risk of developing resistance. Products which can fight biofilm reservoirs in many different production environments are also needed.

A large number of bacteria are associated with undesirable and dangerous biofilm formation, and many of these are suitable for combating with bacteriophages. International work includes extensive and very promising research into the use of bacteriophages in treating antibiotic-resistant Pseudomonas infections in patients with cystic fibrosis.[52,53]

The Norwegian Veterinary Institute has been doing research on biofilm for almost 20 years, and has broad experience with these in a number of pathogenic bacterial species, such as *Salmonella, E. coli, Listeria, Staphylococcus, Pseudomonas* and *Klebsiella*.

Norwegian scientists, industry and regulators have the expertise required to conduct R&D projects for developing bacteriophage-based solutions against biofilm. International collaboration could speed up further expertise enhancement and capacity to deliver


“Where human medicine is concerned, prevention of carrier status and treatment of chronic infection are probably the easiest and most relevant areas of application for bacteriophages.”

Customised regulatory solutions must be put in place

Utilising bacteriophages in people, livestock or food production calls for an evaluation and approval process.

Effective and customised approval pathways are required if bacteriophages are to be developed and adopted on a large scale, both as a supplement to antibiotics and to inhibit their use. These pathways must take account of the characteristics of bacteriophage biology while also helping to encourage the development and commercial use of bacteriophage-based products.

Approval regimes differ between non-medical and medical applications. This chapter covers both in order, and we recommend solutions for the way forward.

Approval of bacteriophage products for non-medical use

Most non-medical applications for bacteriophages relate to controlling undesirable bacteria in food production. These are harmful to plants or animals, causing either loss of food or posing a threat of humans being infected from plants, animals or food.

Approval of bacteriophage products for non-medical use in Norway rests in most cases with the Norwegian Food Safety Authority. Bacteriophages are used today for biocontrol. This is not regulated by legislation and falls under the authority of various government agencies depending on where and how the product is utilised.

The only bacteriophage product currently used in Norway is Stim's CUSTUS®$_{YRS}$, which is utilised in Norwegian salmon farming to control infection pressure by the *Yersinia ruckeri* bacterium in farm water.

Since this water comes into contact with farmed fish, the Food Safety Authority is responsible for evaluating the method and declaring it safe. In addition, the product's seller must document that its effect complies with section 3 of the Norwegian Marketing Act and with the Pollution Control Act if usage releases bacteriophages which could harm the environment.

Using bacteriophages under the definition of "biocontrol" functions well for a number of applications, but could be vulnerable to misuse by unscrupulous players. Guidelines for evaluating new bacteriophage products at the Food Safety Authority and other relevant regulators should prevent undesirable use.

The USA has a separate approval regime for non-medical applications. Bacteriophages used in aquaculture, agriculture and food safety are approved under the generally recognised as safe (Gras) regime. This designation is used by the Food and Drug Administration (FDA) for substances considered to be safe for adding to food. They are exempt from the tolerance requirements of the federal Food, Drug and Cosmetics Act for food additives.[54]

No similar solution for bacteriophages is found in the EU, but could be established in Norway through the Food Safety Authority, the authority's specialist resources and the Norwegian Scientific Committee for Food and the Environment (VKM).

Recommendation 5 Increased expertise about and establishment of regulatory practice on non-medical use

We recommend that the Norwegian Food Safety Authority strengthens its expertise with bacteriophages and establishes a practice for approving bacteriophage-based products in non-medical areas of application. This can be achieved by creating a specialist group on bacteriophages which establishes, in cooperation with relevant specialists and also possibly with the Norwegian Scientific Committee for Food and Environment (VKM), routines for evaluating and approving the quality and safety of bacteriophage-based products. Potentially dangerous applications of bacteriophages can thereby be excluded.

Approval of bacteriophages for medical use

Two regulatory pathways are currently available in Norway for approving products for medical use.

1. Approval and marketing licence from the Norwegian Medicines Agency following clinical trials of a medicine.

2. Individually customised treatment with bacteriophages under a doctor's prescription for a medicine which must be prepared by a pharmacy pursuant to Norway's Pharmacy Act and pharmacy regulations.

It is unclear whether these approval regimes are suitable, or whether separate regulations customised to a bacteriophage's restricted host spectrum and mode of operation are required.

Bacteriophage-based medicines with marketing licence

Pursuant to the Norwegian Medicines Act, all medicines "produced industrially or by an industrial process" must have a marketing licence (ML) before they can be legally sold. This is awarded on the basis of extensive documentation concerning quality, safety and efficacy, in accordance with guidelines prepared by the Norwegian and European medicines agencies.

The path to an ML represents a very large investment in R&D for companies developing medicines. A study recently published in the Journal of the American Medical Association reports a mean cost of USD 985 million and an average of NOK 1.3 billion.[55] Such investments require a large and long-lasting market for the product being developed. The narrow host spectrum for

bacteriophages means that they cannot individually achieve a market value which could justify investing billions in R&D.

Two primary challenges must be overcome if bacteriophage-based products are to be developed up to receipt of an ML.

1. Today's guidelines on documentation for an ML application were originally developed for chemical medications. Guidelines have subsequently been produced for various types of chemical medications which have great transfer value for documenting the quality and safety of bacteriophages. It has nevertheless proved very difficult to produce efficacy documentation for bacteriophages which accords with today's guidelines for efficacy studies.[56] Guidelines are required on conducting clinical studies as well as documenting pharmacokinetics and efficacy which take account of the bacteriophage mode of operation as self-propagating "live" biological entities with narrow host spectra.

2. 2A bacterial illness can be caused by a large number of different variants of the pathogenic bacterium. The narrow host spectra of bacteriophages therefore make it challenging to develop medicines with a sufficiently large and long-lasting market to justify an ML application. Such products must comprise a large number of different bacteriophages in order to be effective against a significant proportion of the bacterium's variants. Since only a few of the bacteriophages included will be effective for each case or patient, a product composed of a large number of bacteriophages could become (unnecessarily) expensive. To ensure a long-lasting market for the product, moreover, its bacteriophage composition will need to be updated in line with changes in the target bacterium's diversity – through, for example, the import of new variants to the geographical area covered by the ML.

Regimes should be developed which make it possible to adapt which of the bacteriophages in the product are given to each patient, and regimes must be developed for effective updating of the product with new bacteriophages in order to ensure that it remains effective against the diversity of the target bacterium at any given time – while also ensuring that costs associated with approval allow private companies to invest in bacteriophage-based medicines.

Use of bacteriophages through doctor's prescriptions for preparation by a pharmacy

Challenges presented by developing and approving bacteriophage-based medicines with an ML, particularly the need to adapt which bacteriophages are given for each patient or outbreak of illness, prompted the creation in 2018 of the pathway based on a doctor's prescription for preparation by a pharmacy.[57]

Pursuant to the Pharmacy Act and the regulations on preparing medicines in pharmacies, the preparing pharmacy undertakes to prepare the medicine prescribed by the doctor. Applying this regulation to bacteriophages will require medical practices or centres with the necessary expertise to prescribe the correct bacteriophages for each patient as well as the establishment of quality standards and pharmacies which are capable of producing the correct bacteriophages in accordance with these requirements.

Recommendation 6 Establishing an effective approval system for medical use

No country currently has effective systems to approve bacteriophages for medical use. The Norwegian Medicines Agency already has the necessary expertise with these viruses and the capabilities required to develop a regime which allows them to be adopted quickly for treating bacterial illnesses in people. It is also envisaged that such a regime could provide a model for other national and international health authorities.

We recommend that the Ministry of Health and Care Services asks the Norwegian Medicines Agency to study the opportunities offered by current regulations and possibly to identify new and effective approval regimes which make provision for adopting bacteriophages as an effective alternative to antibiotics.

Recommendation 7 Establishing a cross-disciplinary group to evaluate and develop regulatory solutions

We recommend the appointment of a cross-disciplinary group with expertise in human and veterinary medical microbiology, bacteriophage biology and business development, as well as regulatory/legal expertise on documenting the quality, safety and efficacy of medicines, in order to support the planning and execution of the R&D projects recommended in this report. Such an arrangement will make it possible to evaluate and develop regulatory solutions at a detailed level while the projects are under way.

Mandate of the work group

Purpose
The purpose of the work is to identify specific proposals for the way bacteriophages could provide a solution in the fight against antibiotic resistance.

Assignments
The work group will:

- provide an overview based on the current state of knowledge about opportunities with and limitations of bacteriophages
- identify possible bacterial indications, human and veterinarian, which should be given priority in future R&D commitments
- identify R&D challenges and concretise possible collaboration projects between academic, the health care industry and the health trusts which could develop real and implementable areas of application for bacteriophages
- propose changed regulatory solutions covering the various areas of application for bacteriophages.

Approach
The work group will have an open approach and invite relevant players – such as the Norwegian Medicines Agency, the Norwegian Food Safety Authority, the Research Council of Norway and Innovation Norway – to dialogue and meetings as and when required.

The work group will hold two working meetings as well as a final meeting to review the report.

The physical meetings will be held in Tromsø, or in Oslo if required.

Hans Petter Kleppen (Stim) will lead the secretariat, which will make preparations for the meetings in collaboration with the chair of the work group. The agenda will be circulated one week in advance. Following the meeting, the secretariat will circulate a brief summary with action points and the division of responsibility for further work.

The secretariat will handle most of the writing in close dialogue with the work group. A first draft of the report will be completed for the final meeting of the work group.

Report and time frame
The work will conclude with a brief report from the work group (about 10 pages). It will be completed by *31 March 2021*. The report will then be typeset and a desired number of copies printed.

The report will be submitted to the prime minister in *April 2021*.

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