NORWEGIAN MINISTRIES

Strategy

National Strategy against

Antibiotic Resistance 2015–2020

***Staphyococcus aureus* with different patterns of resistance on an agar plate.**

Strategy

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Antibiotic Resistance 2015–2020

Preface:

A threat to modern medicine

If we are to maintain antibiotics as a global common good for coming generations, we must set ambitious goals for the struggle against antibiotic resistance. Today, antibiotic resistance is a rapidly growing problem around the world and a serious threat to global health. We are at risk of a future without effective antibiotics, in which infections that today are considered low risk once again have deadly outcomes.

The threat of antibiotic resistance cannot be eliminated, but we need to put mechanisms in place to minimize the risk that resistance will emerge, while setting in place approaches that will minimize the health consequences of resistance to humans and animals. This calls for renewed efforts across several sectors. Norway has a low use of antibiotics compared with many other countries, but we can nevertheless improve further.

The fight against antibiotic resistance calls for international cooperation. We must see to it that new antibiotics and diagnostics are developed. And we must see to it that antibiotics are used only when they are necessary, while assuring that all who need antibiotics can get them.

The Norwegian National Strategy Against Antibiotic Resistance 2015-2020 lays out the Government's goals for work over the coming years and the steps needed to achieve these.

Oslo, June 2015

Photo: Bjørn Stuedal

Photo: Paul Paiewonsky

Photo: Torbjørn Tandberg

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Introduction

Antibiotics[1] are a global common good that we need to preserve for future generations.

Over the past 75 years we have had effective antibiotics that have had enormous impact on limiting infectious diseases and have been an essential aspect of modern medical care. The biological mechanisms for developing resistance to antibiotics are common in bacteria. This is why Sir Alexander Fleming in his 1945 acceptance speech for the Nobel Prize in Medicine warned about the dangers of overuse of penicillin. We now have solid evidence that use of antibiotics leads to growing resistance.

Antibiotic resistance is now a rapidly expanding problem around the world and is causing a serious threat to global health. The World Health Organization (WHO) stated in 2012 that this is one of the greatest health threats facing the world. The expansion of antibiotic resistance is made even more serious by the stagnation in the development of new antimicrobial drugs. We are therefore at risk of a future in which infections that today are considered minor could again emerge as serious health threats and a major cause of deaths.

It is not possible today for just one or even several countries together to isolate themselves from what is happening elsewhere in the world. Antibiotic resistance moves freely across the boundaries between commerce, food, people, animals and the environment, and requires a global response. We all have a common interest in the responsible use of antibiotics, so that existing and future antibiotics will remain effective.

In the global context, we have a moral responsibility to assure that all have access to antibiotics when there is a real need. We also have a common interest in the development of new antibiotics at a faster pace than currently, so that we can stay on the cutting edge of development. To achieve this, we need a stronger international normative foundation in order that as many countries as possible pursue policies that reduce the risks associated with antibiotic resistance.

Effective antibiotics are a necessity for modern medical treatment; they have a role in all situations in which infections can result in a poor outcome, such as cancer treatment, neonatal medicine, in transplant surgery or a range of common surgical procedures where antibiotics are used to minimize the risk of infection. Without effective antibiotics the risks of doing such procedures can grow to unacceptable levels. This is in addition to necessary use of antibiotics for serious bacterial infections such as pneumonia and meningitis.

Norway has among the lowest use of antibiotics to animals in all of Europe. In aquaculture the introduction of effective vaccines has reduced antibiotic use by 99 percent in total weight since 1987, while Norwegian fish production has increased more than 20-fold during that same time period. Even though Norwegian animal husbandry and food production are in good shape, there are nevertheless been instances of antibiotic resistance in some livestocks of Norwegian poultry and swine.

1 Antibiotics are pharmaceutical drugs that kill bacteria or slow bacterial growth, and are used to prevent or treat infections. Antibiotic resistance results in bacteria that are no longer controlled by antibiotics.

"In the global context we have a moral responsibility assure the greatest possible access to antibiotics when they are needed."

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Today we have limited understanding concerning the environment's effect on the development of resistance. Previously, it was believed that the spread of resistance was principally from the human environment to nature. New studies indicate that nature can also be a source for the development of resistance. To understand how nature can spread resistance to various environments, it will be important to map the presence of resistance in the bacterial population in soil, fresh water, the ocean, sediments, wild and domestic animals. Based on such mapping it will be possible to develop management strategies and put in place efforts to prevent and monitor the spread of resistance.

The strong connections between human, animal, and fish health and the environment call for a cross-disciplinary approach.[2] This strategy therefore aims to examine in a holistic way the use of antibiotics and other drivers of resistance, the development and spread of resistance among humans, animals, in food and in the natural environment. It provides guidance up to 2020 for joint efforts against antibiotic resistance, with concrete goals and action steps.

The main goal of this strategy is to reduce the total use of antibiotics and to assure responsible use of antibiotics in all sectors, to increase the body of scientific knowledge, and to be an international mobilizer against antibiotic resistance.

This strategy is based on an August 2014 report from a cross-sectoral expert group: *Antibiotic Resistance – knowledge gaps, challenges and current efforts*.[3]

This strategy is consistent with the Global Action Plan against antibiotic resistance that was approved at the World Health Assembly in May 2015[4] and a resolution from FAO in June 2015.[5]

Action plans for various aspects of this strategy will be developed.

2 This is known as the One-Health approach.

3 http://www.fhi.no/dokumenter/35ed0e4c20.pdf

4 http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_20-en.pdf

5 http://www.fao.org/3/a-mm736rev1e.pdf

1 GOALS

In order for antibiotics to remain a common global good for future generations, we need to set ambitious goals for our work against antibiotic resistance. The Government has established a mix of overarching and sector-specific goals. The overarching and sector-specific goals are mutually reinforcing. The goals for each of the sector-specific areas have been developed to be measurable and verifiable.

Overarching goals for the period 2015–2020

1. Reduce the total use of antibiotics.
2. More appropriate use of antibiotics.
3. Improved knowledge of what drives the development and spread of antibiotic resistance.
4. Be a driver in international and normative work to improve access, responsible use, and development of new antibiotics, vaccines and better diagnostic tools.

Sector-specific goals for the period of the strategy

Health:

1. Antibiotic use in the total inhabitants will be reduced by 30 percent, measured in DDD[6]/1000 inhabitants/day, as compared with 2012.
2. Norway will be one of the three European countries that uses the least antibiotics in humans, measured in DDD/1000 inhabitants/day.
3. Prescription of antibiotics will be reduced from an average today of 450 prescriptions per 1000 inhabitants per year to 250 prescriptions per 1000 inhabitants per year.
4. Prescription of antibiotics for respiratory infections will be reduced by 20 percent, measured in DDD/1000 inhabitants/day, compared to 2012.
5. Studies will be carried out on the burden of disease as a consequence of antibiotic resistance, as a consequence of possibly too little antibiotic use, and the effect of infection control measures.

Food producing animals and household pets:

1. Mapping of resevoirs of antibiotic resistant bacteria will be carried out in the most relevant animal populations and plants important to food safety.
2. LA-MRSA will not be established in the Norwegian pig population.
3. ESBL in the Norwegian poultry-production will be reduced to a minimum.
4. The use of antibiotics in terrestrial animals used for food production will be reduced by at least 10 percent compared with 2013.
5. The use of antibiotics in household pets will be reduced by at least 30 percent compared with 2013.
6. Narasin and other coccidiostats with antibacterial properties will be phased out of chicken production, as long as this does not adversely affect animal health and well-being, and does not result in increased use of antibiotics for treatment of infections.

Fish:

7. Total antibiotic use in fish farming in 2020 will be at the same or lower levels than for the period 2004-2014, measured in total kilograms of antibiotics.

Climate and environment:

1. Mapping of antibiotic resistant bacteria will be carried out in representative environments and selected organisms in animals, water and soil with varying degrees of exposure to antibiotics.
2. Studies will be initiated to explore the effect in nature of other drivers of resistance, including disinfectants, biocides and heavy metals.

6 Defined Daily Doses

2 FOCUS AREAS

While risks associated with increasing antibiotic resistance cannot be eliminated, we need to reduce its occurrence while minimizing the consequences of resistance on human and animal health. The Government intends to accomplish this through better scientific understanding and by increasing the understanding among both prescribers and the general public about antibiotics and their use. We must improve our efforts at improving hygiene in hospitals, nursing homes and in society, and we must assure that the current good practices concerning antibiotic use in animals is well maintained.

At the same time, we must contribute to international efforts against increasing levels of antibiotic resistance through i) working towards binding agreements that assure that all who need access to antibiotics receive them, ii) that antibiotics are only used when they are needed, and iii) that we will get access to new antibiotics and diagnostic tools so that future generations also will have access to these life-saving medicines when they are needed.

2.1. Strengthen scientific understanding

A considerable effort is needed to generate a better and more comprehensive understanding of the extent of antibiotic resistance in humans, food, animals and in the environment. The issue of resistance is complex and calls for a better scientific knowledge base so that we can have a comprehensive view of the human and natural factors that limit or encourage the development of resistance. For instance, little is understood about where and how resistance arises and is spread among bacteria in various ecological niches, or whether combinations of resistance factors are maintained or change over time.

We need better scientific understanding concerning the degree of antibiotic resistance to be found in various environments. Such mapping needs to be carried out on a regular basis in order to follow development and spread, and is essential for assessing the impact of measures to limit its development. New mapping efforts need to be established in numerous areas, and we need to expand current monitoring efforts.

We lack systems for real-time monitoring of resistance both in human and veterinary medicine, which would provide great opportunities in linking data concerning antibiotic use with the emergence of resistance. Such linking of data will eneable the discovery of new trends in prescription and the associated changes in the emergence of resistance.

There is a lack of knowledge of the spread of resistance genes through food and what risks this creates for consumers. This relates both to Norwegian and imported foods. There is also a lack of knowledge of which fact can best reduce continued carriage of resistant bacteria among infected individuals.

The government will:

- carry out mapping of antibiotic resistant bacteria in humans, in food, in relevant animal populations and in sentinel environments.
- assess whether to expand the Prescription Register, establish a national microbiological data base, and develop a better suited set of regulations, thereby assuring better real-time access to data.
- assess the establishment of a project to set up a national microbiological data base, with the purpose of continuous monitoring of instances of antibiotic resistance and the occurrence of microbes that often lead to inappropriate use of antibiotics.
- assess whether new infection control measures are warranted in the overall food chain, including in the risk assessment carried out by the Scientific Committee for Food Safety (VKM).
- assess the need for changing recommendations concerning kitchen hygiene and risk communications on food handling in the context of emergence of resistant bacteria.

EXAMPLE

In a joint report from January 2015, the European Center for Disease Control (ECDC), the European Food Security Administration (EFSA) and the European Medicines Administration (EMA) confirmed the relationship between the use of antibiotics and the development of resistant bacteria. The report also shows that the use of antibiotics in animals can lead to resistance among humans. This reaffirms that that the problem of antibiotic resistance must be addressed through strong cooperation between the various sectors.

More needs to be known about the importance of sanitation and the management of fertilizer to prevent the spread of resistance, either presently seen or emerging. This is as true on the human side as on the animal, where the consequences of the use of manure as fertilizer and its runoff into the environment for the development of resistance are not well understood. Research is needed concerning how best to spread fertilizer without spreading resistance.

It will be useful to research the impact on antibiotic resistance of the systematic use of food additives, including other drugs aside from those classified as antibiotics – for example, zinc and copper which are added to swine and poultry feed, as well as coccidiostats added to poultry feed.

Other chemicals (including disinfectants, biocides and heavy metals) can lead to emergence of resistance. To establish optimal strategies, it is important to understand which chemicals are especially strongly associated with increased resistance. We also need to establish a program of basic research to understand the biological mechanisms underlying these effects.

The Government will:

- in coordination with the business community, start the process to phase out the use of narasin as a food additive for poultry, as long as this does not have a negative effect on animal health and well-being or lead to greater use of antibiotics for treatment.
- initiate studies to explore the effects of resistance-promotors other than antibiotics, including disinfectants, biocides and heavy metals, in the natural environment.

Work has been carried internationally regarding the economic costs of antibiotic resistance. Corresponding analyses need to be carried out nationally to better understand the disease burden and associated costs, which can serve as the basis for future work.

In the spring of 2014 a socioeconomic analysis was carried out on the costs of LA-MRSA (livestock-associated methicillin resistant *Staphyococcus aureus*) in swine. The analysis was carried out over a short time period, and the Veterinary Institute has initiated a study to validate and further develop the dispersion models on which it was based. The results of this study will be available in 2015/2016. Subsequently, these types of models can also be used in other work, such to assess the impact that a given intervention has on the development and spread of resistance among swine herds. Other similar impact studies will also be needed on additional types of resistant bacteria.

The government will:

- assure that studies are carried out on the burden of disease resulting from antibiotic resistance and associated economic costs.

2.2. Improve the level of understanding and competence regarding the use of antibiotics, among the general population as well as among prescribers

General population

Government authorities are responsible for assuring general understanding of and respect for the use of antibacterials. Prescribing doctors, dentists and veterinarians are responsible for appropriate clinical diagnosis and for assessing whether treatment with antibiotics is necessary and prudent. Prescribers must take responsibility for explaining to their patients and customers why and when antibiotics should not be used. They must also explain when and how antibiotics should be used and assure appropriate use. The general public must be provided with better information about appropriate use of antibiotics and the development of antibiotic resistance so that individual patients and those around them do not insist that doctors, dentists and veterinarians provide inappropriate antibiotic prescriptions. Mass media campaigns to educate the public about antibiotic resistance have been carried out in Belgium and France with positive results.

The Government will:

- see to it that the public is well informed about appropriate use of antibiotics
- evaluate mass media campaigns for the general public aimed at preventing unnecessary antibiotic use

Doctors, dentists, veterinarians and aqua medicine biologists

In Norway, emphasis in the training of those who will have prescribing authority is already placed on limiting the use of antibiotics. Therapeutic guidelines in the various workplaces in which doctors, dentists, veterinarians and aqua medicine biologists function are designed to reinforce awareness concerning the use of antibiotics. It is important to follow up these guidelines to assure that they are being adhered to and that new knowledge concerning changing recommendations is translated into practice, including through training courses and other instructional means.

Within the EU there are several countries with more liberal rules about antibiotic use than we have in Norway. Employers are responsible of assuring that the health personnel and veterinary personnel they bring to Norway to work are well versed in the relevant professional guidelines. Employers are responsible for assuring that their employees have been trained regarding official guidelines on prescribing antibiotics; this is part of their obligation to assure responsible performance among those they hire. In assessing employers' performance, it is appropriate to assess if their training efforts are risk-based and are developed, carried out and maintained consistent with official internal control systems.

Official regulations concerning infection prevention in health and support services include requirements that institutions' infection control programs shall include written guidelines on the use of antibiotics. The managment of these institutions and companies must assure that infection control programs are an integral part of their internal quality control systems.

The government will:

- carry out county by county infection control conferences for municipality physicians and other health personnel within the municipality health and care services, with particular attention to technical guidelines for prescription of antibiotics.
- carry out oversight of employers' actual performance in training their employees about technical guidelines for prescription of antibiotics.

2.3. Improve prescribing practices in all sectors

Diagnostic codes on antibiotic prescriptions for humans

To assure good monitoring of prescriptions, good prescription registers are an important tool. These registers currently provide good oversight concerning the use of various antibiotics with respect to age, sex and geographic location. However, they do not include information concerning diagnoses, so it is not currently possible to determine which antibiotics are used against various infections in humans. This makes

it difficult to assess whether current prescribing practices are consistent with the recommendations in the guidelines. By requiring diagnostic codes on all prescriptions, or by finding another way to assure that information about diagnosis is included in the Prescription Register, these registers would be able to provide statistics useful for quality assurance of antibiotic usage, management and planning.

Alternatively, it might be possible to solve this without having the pharmacist see the diagnostic code at the time they fill the prescription, while still assuring that this information ends up in the Prescription Register. Pharmacy workers do not have a need to see confidential diagnostic information. In any event, it will be necessary to put in place technical modifications. The Health Directorate is hereby asked by the Health and Care Department to explore and lay out by the middle of 2015 what technical and legal changes would be called for.

Furthermore, the use of diagnostic codes could be useful in providing feedback to prescribers and to improve overall understanding of patterns of prescribing within professional discussions. Doctors will use this information as the basis of internal controls and quality improvement.[7]

7 Meld. St.28(2014-2015) Prescription Notice. Correct use – better health

Guidelines and normative work

Updated therapeutic recommendations and norms are important contributors to maintain the good prescribing practices that are generally the rule in Norway. It is important to have up-to-date and accurate information concerning antibiotics and resistance as a part of professional training, where the foundation for prescribing practices is formed. This will lead to lower levels of prescribing in the long term.

Doctors and veterinarians who are trained in other countries are not necessarily trained with the same restrictive use of antibiotics and other drugs as in Norway. Since the opportunities are limited for additional formal coursing as a requirement for working in Norway, it will be necessary to find means that will lead most practitioners to carry out desired practices. This is an area that requires follow up and where efforts to improve competency need to be assessed.

Changes of norms can be challenging, but studies show that prescribing practices can be permanently influenced through professional association reviews of individual prescribing practices. The antibiotic center for primary health care has carried out studies that show that when general practitioners present and discuss their own prescribing practices, this results in an overall decrease in prescriptions. This approach

EXPLANATION

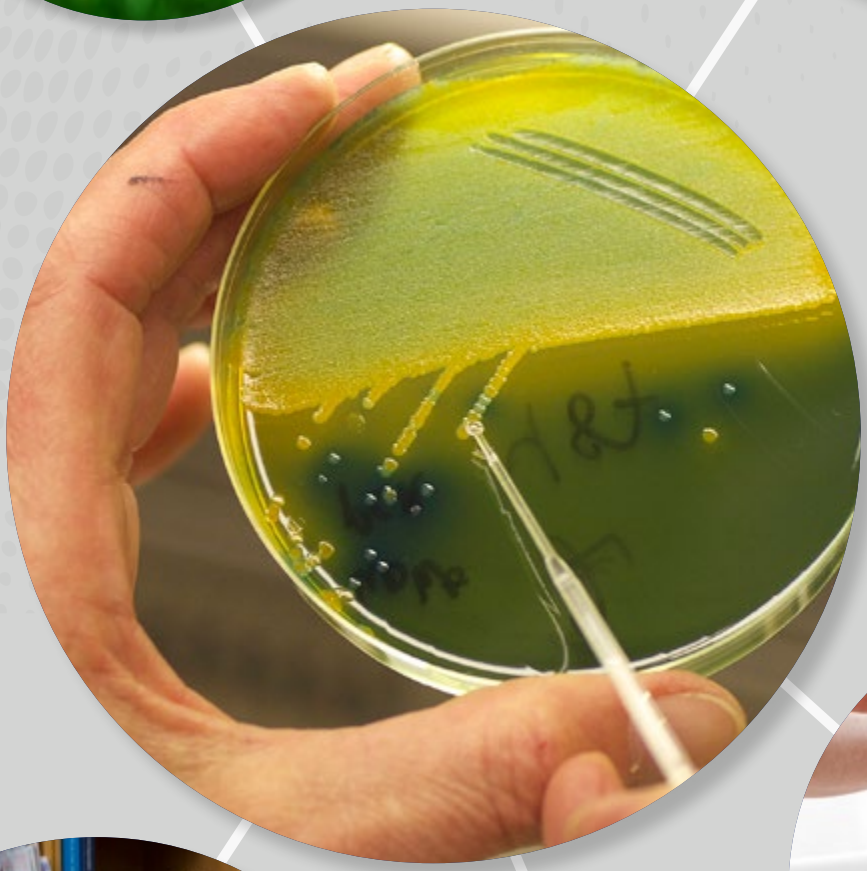
Narrow spectrum and broad spectrum antibiotics

There are many different bacteria that lead to infections. Most antibiotics only affect only a portion of these bacteria. Antibiotics that affect a wide range of bacteria are considered broad spectrum, while those that affect a smaller group of bacteria are considered narrow spectrum.

When antibiotics are needed, it is preferable to use antibiotics with a narrow spectrum that do not affect the normal protective bacterial flora in our bodies, but that kill only the bacteria causing a particular illness.

Each time an antibiotic treatment does not kill all the disease-causing bacteria, those bacteria with the greatest resistance are the ones that survive. This can happen if treatment is ended too soon, or if the dosage is too low. There is a risk then that the illness may recur. The surviving bacteria may have developed resistance against the medicine used earlier and may call for another antibiotic to be used.

When bacteria that are sensitive to narrow spectrum antibiotics develop resistance, it may be necessary to use broader spectrum antibiotics. This leads to increased natural selection for the further development of resistance against these broad spectrum antibiotics. This can result in multi-resistant disease-causing bacteria that cannot be treated.



should be assessed to see if it can be widely used for all the country's general practitioners.

When antibiotic treatment is needed, it is essential that prescribers use drugs with the narrowest possible spectrum (see box). Responsible use should follow technical guidelines for the use of antibiotics. The focus on responsible use must be expanded to maintain current good practices in Norway.

Medicines and animal health

The veterinary medicine register (VetReg), which was established in 2011, will be developed so that animal health personnel can see their colleagues' prescribing practices, similar to what is planned for doctors. Support for other colleagues' prescribing practices will also help animal health professionals to withstand potential pressure from animal owners who demand special medicines. Improved understanding of appropriate use of antibiotics among animal owners will reduce the pressures put on prescribers.

Official authorities work through the Norwegian Food Safety Authority (Mattilsynet) to assure good and appropriate prescription practices among veterinarians and aqua medicine biologists who work in fish farming. VetReg will be part of a planned campaign in the autumn of 2015 which will review the prescribing practices of aqua medicine biologists. This review will include specific prescribing practices with the medicines and diagnoses noted on the prescription, as well as whether the guidelines established by the authorities are being followed and possible effects on the environment. At the same time, the Food Safety Authority will carry out a thorough review of its tools for handling data reported through VetReg. This campaign will also assist in developing better guidelines for the use of medicines in fish.

The role of the County Governor, the Norwegian Board of Health Supervision and the Norwegian Food Safety Authority

The County Governor's Office and the Norwegian Board of Health Supervision (NBHS) deal with complaints against or concerns relating to the conduct of healthcare personnel submitted by patients, their families or others. The County Governor may identify breaches of duty and issue guidance. More serious cases are passed on to the NBHS, which can impose administrative reactions, such as warnings or the withdrawal or limitation of authorizations to practice.

Questions relating to the overuse of antibiotics in the treatment of one or more patients may be the primary issue in a disciplinary case, or be part of a broader complex of concerns. The NBHS's assessment compares the latest medical research, national guidelines and information, including that derived from patient notes regarding how that knowledge is applied and adapted to the individual patient. The national guidelines for antibiotic use are a key point of reference when dealing with disciplinary cases relating to the prescribing of antibiotics.

The Norwegian Food Safety Authority (NFSA) monitors the activities of animal health personnel to ensure they comply with the Act Relating to Veterinarians and Other Animal Health Personnel. Veterinarians, fish health biologists and veterinary nurses are defined as animal health personnel under the provisions of the act. Supervision is implemented either in the form of planned inspections or as follow-up to notices regarding alleged breaches of duty that the NFSA receives. Should any such investigation uncover failures to comply with the regulations, the NFSA may follow up by ordering the animal health worker to change their practices to bring them into compliance with the law. Serious, wide-ranging or repeated violations of the regulations may result in the animal health worker being given a warning, or in them losing their entitlement to prescribe or authorization to practice. The matter may also be reported to the police.

The government will:

- introduce a requirement to include a diagnostic code on all antibiotic prescriptions for people.
- investigate the creation of a system for feedback to GPs and animal health personnel with regard to the use of antibiotics in their own practices, including the offer of peer assessment of antibiotic prescribing practices.
- ensure that guidelines for the use of antibiotics are up-to-date, and that information campaigns lead to compliance with the recommendations, in conjunction with relevant professional bodies within the human and animal health sectors.
- assess how the supervisory authorities may participate more actively in the effort to combat antibiotic resistance.

2.4. Improved infection control

Infection prevention and control measures

General protection against the spread of infection is an important part of the preventive health effort, and is firmly embedded in the Norwegian legislative and regulatory framework. The regulations relating to the control of infectious diseases stipulate that all institutions included in the municipal health and social care service, as well as the specialist health service, shall have an infection control program. The infection control program shall be adapted to the individual undertaking, and shall be based on a risk assessment and identification of critical points in the institution, including the prevention and control of serious infections caused by antibiotic resistant bacteria.

The consequences of the spread of antibiotic resistant bacteria to the specialist health service and the municipal health and social care service will be severe. A particular focus on infection prevention within the health service is therefore necessary. The efforts of the health service to prevent the spread of antibiotic resistant infections are today largely based on measures directed against specific microbes, such as MRSA. However, the development of antibiotic resistance requires a reinforcement of infection prevention activities in all areas of society. There are sound reasons to believe that, confronted with growing levels of antibiotic resistance, general measures, such as good hand hygiene, will be even more important for both the health service and the general population. There is a need for increased competence about and enhanced implementation of infection prevention measures, both in the population and in the health service.

In the area of animal health, we need an overarching emergency response to control not only diseases caused by resistant bacteria in Norway, but also diseases which may be brought into the country from abroad. Local competence must be available to perform the correct tests in the field. Veterinarians in private practice must form the front line of any emergency response. This assumes that there is direct contact between veterinarians in the field, the NFSA and the Veterinary Institute.

The government will:

- improve the monitoring and analysis of incidences of resistant bacteria, both in clinical isolates (from infections), capacity of the healthy portion of the population to act as carriers and, in particular, incidences of infection associated with the health services.
- ensure that studies are carried out of the effectiveness of general infection prevention and control measures.

Vaccines

Increased use of vaccines could reduce the number of infections, and thereby the ease with which they can spread. Although the development of new vaccines for people, animals and fish is important, improved use of existing vaccines could reduce the burden of disease, thereby decreasing the need for antibiotics as fewer individuals become ill. The use of vaccines, including those against viral diseases, is important to reduce general ill-health.

The development of specific vaccines in connection with outbreaks of disease in livestock populations may reduce the extent and duration of the outbreak. This reduces the time during which antibiotics must be used, thus diminishing the selective pressure.

EXAMPLE

More extensive vaccination coverage against seasonal influenza, both among health workers and vulnerable groups, could reduce the number of cases. As a result, fewer influenza sufferers will contract bacterial complications (which must often be treated with antibiotics), and there will be fewer incorrect diagnoses, i.e. that influenza (for which antibiotics should not be prescribed) is confused with the symptoms of a bacterial infection.

The government will:

- reinforce efforts among the general population to ensure a high degree of vaccination coverage through the publicly funded vaccination program.
- support efforts to develop new and better vaccines.

Rapid and accurate diagnosis

The development and application of new diagnostic methods is an important area to focus on if improved and more accurate diagnosis of infectious diseases, and therefore more appropriate antibiotic treatment, is to be achieved. More accurate microbiological diagnostics could substantially reduce the prescription of antibiotics. In people, this may apply particularly to respiratory infections, which are often caused by a virus, but whose symptoms are difficult to distinguish from a bacterial infection. Such rapid and reliable diagnosis must be expected to incur costs, but if the result is fewer sick individuals and a reduction in the spread of the infection, it will be a good investment.

In the veterinary field, there must be a duty to report and a central organization capable of receiving such notices and, where necessary, providing information to avoid the spread of infection. If public laboratories with broad professional competence are replaced by highly specialized private laboratories, society could lose the opportunity for early diagnosis which, in many cases, can be decisive for the infection control situation we have in Norway.

The government will:

- help to develop better diagnostic methods for infectious diseases and alternative treatment strategies in the areas of both human and animal health, through participation in international research collaborations.

2.5. Treat and eradicate infections caused by resistant bacteria

Today, the primary purpose of screening humans at risk of being carriers of MRSA is not only to prevent the spread of infection, but to eradicate the organism in the carriers themselves, where possible and appropriate.

The presence of LA-MRSA in the pig population has little impact on the animals themselves, but can be extremely serious for humans. Since the first outbreak in 2013, the authorities have therefore pursued an ambitious strategy to try and prevent pig herds becoming centers of concentration of the bacteria. Although it is too early to say whether it will be possible to prevent the bacteria from establishing themselves in pig herds, efforts must be made to keep levels as low as possible. If the mapping of concentration points in various environments reveals antibiotic resistant microbes, necessary measures will have to be implemented.

The government will:

- assess the expedience of screening for other selected microbial resistance properties, in addition to methicillin-resistant *Staphylococcus aureus* (MRSA), in connection with admission to healthcare institutions.
- implement measures to cleanse environments of concentrations of resistant bacteria, if new knowledge and cost/benefit evaluations indicate this would be expedient.
- work to ensure that LA-MRSA does not establish itself in the Norwegian pig populations.

2.6. Strengthen normative international collaboration

Antibiotic resistance is not a challenge that can be resolved nationally. Resistant bacteria from other parts of the world may also find their way to Norway. A long-lasting and effective international response is a prerequisite for sustainable results in Norway.

The situation in different countries around the world varies substantially with regard to prescription practices and access to antibiotics. Some people will use too little or experience a lack of availability, e.g. due to poor healthcare provision or poverty. Some may use antibiotics too much or incorrectly, while others may be exposed to counterfeit antibiotics. In such cases, the dosage may be incorrect, leading to the development of resistance. Such scenarios frequently occur at the same time within the same country. Along with stagnation in the development of new antibiotics, lack of access and irresponsible use are the most important challenges.

A joint international effort is therefore needed to reinforce the normative international collaboration, such that as many countries as possible pursue policies that lessen the risks associated with antibiotic resistance. The WHO is the key normative body in the field of human health, and is the natural authority in the fight against antibiotic resistance, in close collaboration with the UN's Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE). Moving forward, Norway will draw on the relevant national professional environments in this international effort. This includes experts on health, agriculture and foreign policy.

Through the processes taking place in the EU, the Nordic countries need to actively support regulations which can help to lessen antibiotic resistance, particularly in the food and veterinary areas. Nordic collaboration via the Nordic Council of Ministers can help to reinforce Nordic collaboration in other international organizations. In many EU countries veterinarians profit financially from the sale of antibiotics, which is unacceptable from a Norwegian point of view.

In addition, efforts should be made to introduce an international ban on the use of antibiotics to enhance growth in food production.

The government will:

- work to strengthen the normative role of the WHO, FAO and OIE in the field of antibiotic resistance, and support the implementation by the organizations and their member states of the measures stipulated in the global action plan, initially in the area of monitoring and surveillance.
- in consultation with other countries, work to promote an approach that combines enhanced access, more responsible use and the development of new antibiotics and diagnostic methods.
- take the initiative to introduce an international ban on the use of antibiotics as growth enhancers.
- work for a ban on veterinarians being able to profit financially from the sale of antibiotics, in an EU context and otherwise where such a ban would be expedient.

Antibiotic resistance has grown to become a central and well-recognized issue in international medical, veterinary and health policy circles. The challenges, however, are less well known in other sectors, e.g. those dealing with trade, finance and foreign policy, as well as emergency preparedness. A precondition for policy changes at the international level is that a sufficient number of different countries, with various regional affiliations and degrees of development, agree on the need for action. In order for countries to build a robust, shared understanding of the problem, a communications effort is required that does not presume prior medical knowledge.

Such a communications campaign should initially be directed at the countries' diplomatic communities in Geneva, Rome, Paris and New York. A shared understanding of the problem among these communities is an important precondition for further efforts to strengthen the internationally normative regulatory regime under UN auspices.

An effective global surveillance system is a necessary

precondition if efforts at the global level to combat antibiotic resistance are to be successful. Any such system will have to build on effective national schemes, which only a few countries currently have and whose quality varies substantially. The objective is to expand today's systems by standardizing, improving and extending the monitoring of both antibiotic use and antibiotic resistance to encompass humans, animals, food and the external environment.

Norway is working to reinforce the monitoring of diseases in developing countries. This includes substantial contributions to the Global Fund, the World Bank's Global Financing Facility and through our contribution to the global safety in healthcare agenda. Antibiotic use and antibiotic resistance should be integrated into this effort, and should be strengthened in parallel with the monitoring of contagious diseases such as tuberculosis and HIV/Aids.

The Norwegian Foreign Service is well aware of domestic conditions in other countries, and can form a picture of the challenges relating to antibiotic resistance in the individual country, based on current news reporting, sources and databases. Since the risk picture for resistance development in Norway largely depends on what is done in other countries, reports from foreign service missions about antibiotic resistance will be useful in the work being done at home.

The government will:

- assess the need to initiate, in collaboration with other agencies, a time-limited international communications campaign to promote understanding of the challenges associated with antibiotic resistance and, through this, create a shared international understanding of the issue beyond the human and animal health, food and agriculture sectors.
- work to extend and standardize the global monitoring of antibiotic use and antibiotic resistance.
- strive to integrate the issue of antibiotic resistance into initiatives relating to disease monitoring and infection prevention to which Norway contributes.
- ensure that selected Norwegian Foreign Service missions provide annual reports on the respective countries' efforts regarding antibiotic resistance.

With many parallel initiatives, it is a challenge to stay up-to-date, and it would be easy for several of them to be duplicated or compete with one another. Which arenas Norway can contribute most effectively to will be kept under constant critical evaluation. At the same time, efforts will be made to ensure that we communicate a consistent message.

2.7. Contribute internationally to the development of vaccines, new antibiotics and diagnostic tools

The development of resistance has created the need for new antibiotics. However, during the last three decades only two new classes of antibiotics[8] have emerged, and few are currently under development. The industry does not consider that there are strong enough incentives to pursue research and development in this field. Antibiotics are only to be used when strictly necessary. When antibiotics are used, it is normally over a short period (days). The industry's complaint, therefore, is that the market is insufficient to recoup the investment cost. Since the development of new antibiotics competes with other development projects aimed at treating chronic illnesses, such as cancer, cardiovascular diseases and dementia, it is to some degree understandable that the industry requires particular incentive arrangements. These should be detached from the antibiotic's sales volume.

The European Commission has invested heavily in research through Horizon 2020 (8th framework program) and contributions to IMI (European Innovative Medicines Initiative's New Drugs 4 Bad Bugs). The latter has, through a private/public collaboration, mobilized almost EUR 3.5 billion for innovation in the period to 2024.

8 Oxazolidinones (Linezolid) and cyclical lipopeptides (Daptomycin)

EXAMPLE

Norway contributes to more sustainable and environment-friendly fish farming in Asia. Vietnam has a substantial aquaculture industry. In 2015, their production of the fish species Pangasius is expected to exceed 1 million tonnes. The pharmaceutical manufacturer Pharmaq became involved in the development of fish vaccines in Vietnam in 2006, and has since developed a fish vaccine that can safeguard the future of this popular Vietnamese fish. The vaccine prevents disease and reduces widespread use of antibiotics. Development of this product was supported by Innovation Norway's IFU scheme (Industrial Research & Development Contracts).

Sweden leads the Council-initiated Joint Programming Initiative on Antimicrobial Resistance (JPI-AMR), in which Norway participates along with 18 European countries and Canada. The purpose is to increase, harmonize and specialize research into antibiotic resistance. So far, the focus has been on the human side, but a broader "one health" perspective is currently under consideration.

In 2015 research funding totaling EUR 9.7 million is being made available, with Norway contributing NOK 4.6 million. So far, this is Norway's most important contribution to research into antibiotic resistance in the human sphere.

The government will:

- participate actively in the international debate about incentive schemes for the development of new antibiotics, while supporting efforts to develop vaccines.
- ensure that Norwegian competence with respect to sustainability and responsible aquaculture is made available to developing countries, including expertise on vaccine development.
- consider increasing contributions to research that can lead to new or better antibiotics and diagnostic methods, including through the JPI-AMR.

EXPLANATION

Joint Programme Initiative on Antimicrobial resistance (JPI-AMR) Strategic Research Agenda, March 2014:

Six pillars:

- Therapeutics (A): Development of novel antibiotics and alternatives for antibiotics - from basic research to the market.
- Diagnostics (B): Design strategies to improve treatment and prevention of infections by developing new diagnostics.
- Surveillance (C): Standardization and extension of surveillance systems to establish a global surveillance program on antibiotic resistance and antibiotic use.
- Transmission (D): Transmission dynamics.
- Environment (E): The role of the environment as a driver for the selection for and spread of AMR.
- Interventions (F): Designing and testing inter- ventions to prevent acquisition, transmission and infection caused by AMR.

2.8. Follow-up and organization of the strategy work

Combating antibiotic resistance requires the efforts of many sectors. The four government ministries behind this strategy have sectoral responsibility for their respective goals and underlying agencies. The Foreign Ministry has overall responsibility for Norway's development and foreign policy. The efforts of the various sectors are mutually interdependent, if the shared goals of the strategy are to be reached. Effective coordination is therefore vital.

The government will:

- continue the interdepartmental working group that will follow up implementation of the strategy.
- review the status at mid-point and towards the end of the strategy period. The last review shall include an update of new knowledge acquired and an assessment of the need for further initiatives.

3 ADMINISTRATIVE AND FINANCIAL CONSEQUENCES

The description of measures is limited to measures that can be implemented within applicable budget frameworks.

4 APPENDIX – CURRENT SITUATION

Resistance to antibiotics is a growing problem both in Norway and worldwide. The trend is unambiguous. These challenges are being experienced in all countries. Compared with other European nations, Norway has a low overall use of antibiotic in animals antibiotics. In Norway antibiotics are not used as growth enhancers in food production. Several European countries use less human antibiotics than we do in Norway, without any detrimental impact on overall health. We can therefore do better. The national systems for monitoring antibiotic resistance are largely in place in Norway, even though we are still facing some major challenges.

4.1. Systems for monitoring antibiotic use and resistance

Human health

Under the Infectious Disease Control Act, the Institute for Public Health (FHI) is responsible for monitoring infectious diseases in Norway and assisting in the international monitoring thereof. The FHI operates the Norwegian Surveillance System for Communicable Diseases (MSIS). This health register is intended to help monitor infectious diseases in people in Norway through the continuous and systematic collection, analysis, interpretation and reporting of information on incidences of communicable diseases. The duty to report applies to around 60 diseases, several of which are associated with antibiotic resistance. This helps to ensure that necessary infection prevention and control measures are implemented.

On the human side, much of the infrastructure needed to monitor antibiotic use and antibiotic resistance, as well as hospital infections, is already in place. Efforts to prevent and limit antibiotic resistance are regulated by means of legislation, statutory regulations and guidelines.

We have a good geographic spread, and collaboration between the various players in the field is good. We monitor:

- resistance to selected clinical isolates through the Norwegian surveillance system for antibiotic resistance in microbes (NORM) in Tromsø,
- incidence surveillance of postoperative wound infections and prevalence surveys of other health-service related infections through the Norwegian surveillance system for antibiotic use and health-service related infections (NOIS)/FHI in Oslo,
- antibiotic use through the wholesalers' database and the prescription register kept by the FHI, and
- the hospitals' pharmaceutical statistics at the National Competence Center for Antibiotic Use in the Specialist Health Service in Bergen.

We have several centres of expertise with regard to antibiotic resistance:

- Antibiotics Centre for Primary Medicine (ASP) in Oslo
- National Competence Centre for Antibiotic Use in the Specialist Health Service in Bergen
- National Competence Service for the Identification of Antibiotic Resistance (K-RES) under the University Hospital of North Norway
- Reference Function for MRSA at St. Olav's Hospital in Trondheim
- The Antibiotics Committee (advises the FHI)
- The Working Group on Antibiotic Resistance (advises the Directorate of Health)

There remains, notwithstanding, considerable potential for improving monitoring and day-to-day analysis on the human side. The surveillance system that has been set up is largely aimed at ongoing infections in people and animals. There is limited surveillance of infections tied to the health service. We lack an overview of how frequently resistance occurs in healthy carriers and which risk factors contribute to the population being colonized by such microbes.

Broad-spectre antibiotics are more often used and at higher doses in hospitals and nursing homes. The moving of patients between institutions can lead to the spread of antibiotic resistance. It is therefore important to obtain a better overview of the consumption of antibiotics at institutions. At present overviews of antibiotic use are found only at the department level in hospitals, while there is no systematic overview of antibiotic consumption in nursing homes.

Animal health

On the veterinary side, too, much of the infrastructure for monitoring antibiotic use and antibiotic resistance is already in place. The field is regulated through legislation, statutory regulations, guidelines and therapy recommendations.

The Norwegian Food Safety Authority (NFSA) has overall responsibility for ensuring compliance with the regulations throughout the entire food production chain. Through the NFSA's monitoring and control programs (OK programs), antibiotic resistance in animals and food is surveyed. The Veterinary Institute is an important partner in the planning and execution of the OK programs.

- Antibiotic use in animals is monitored through the Veterinary Pharmaceutical Register (VetReg).
- Antibiotic resistance is monitored through the Norwegian Surveillance Program for Antibiotic Resistance in Microbes from feed, animals and nutrients (NORM-VET), which was set up in 2000 and is coordinated by the Veterinary Institute.
- The European Commission has initiated the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project. The objective is to gather data on the use of antibiotics at the species level throughout the EU/EEA from 2014. The intention is to enable the identification of potential risk factors for the development and spread of resistance in animal populations.

EXAMPLE OF SURVEILLANCE IN THE ENVIRONMENTAL AREA

In 2014 GenØk launched a research project aimed at identifying the presence of the antibiotic resistant gene nptII in variously exposed soil samples from cultivated fields. The method seems to work. There are plans to take new samples and measurements in 2015. The antibiotic resistance gene nptII has been inserted into a number of genetically modified plants. In connection with this project, GenØk draws on methodologies developed in connection with corresponding investigations in Austria.

4.2. Scale of antibiotic use

There is broad international agreement that antibiotic resistance represents a danger to both human and animal health. However, knowledge of this beyond the healthcare and food production sectors is poor. Despite an awareness of the risk, there may be financial factors which make it attractive to maintain or increase current consumption levels. Data from individual countries show a steady increase in the use of antibiotics in food-producing animals.

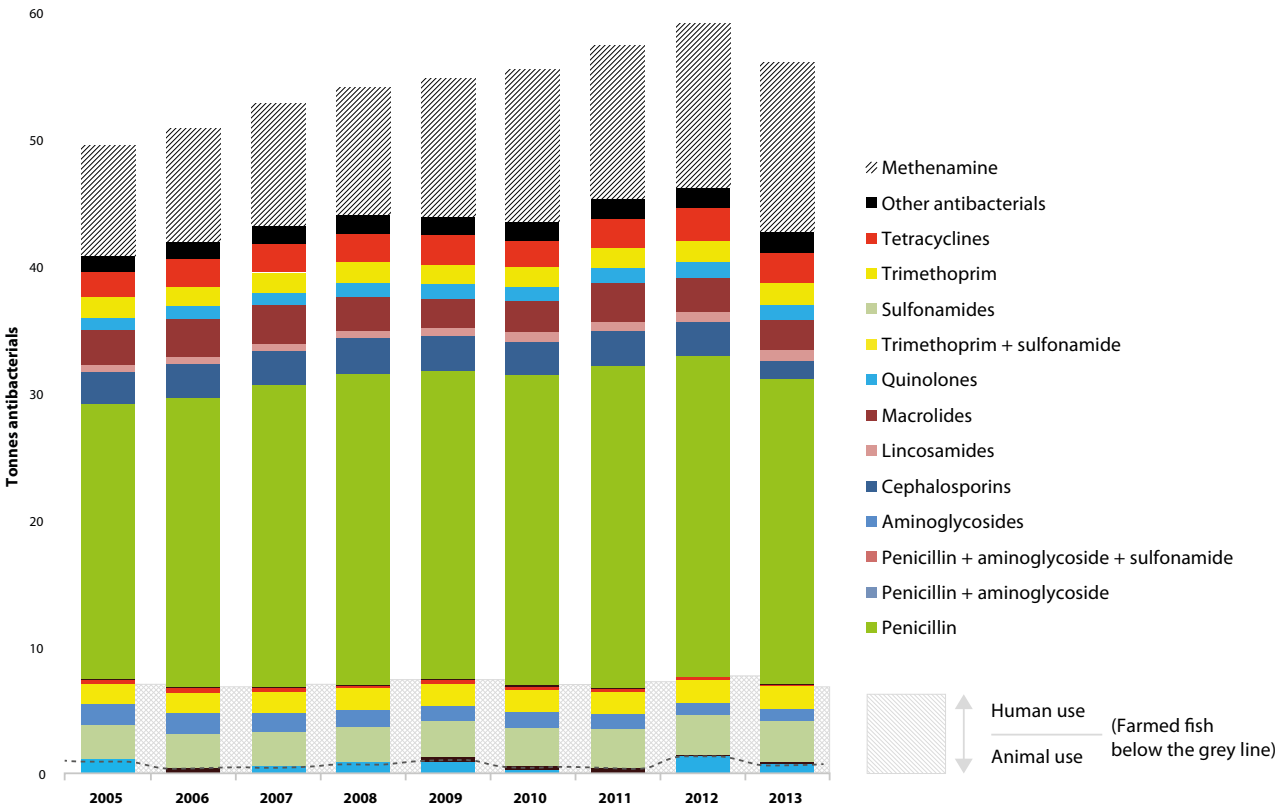
EXAMPLE

The Food and Drug Administration (FDA) in the USA publishes details of the sale and distribution of antibiotics used in food-producing animals. The 2013 report shows that sales in the USA increased by 17 per cent between 2009 and 2013. With regard to antibiotics defined as "medically important", the increase was as high as 20 per cent between 2009 and 2013.

Worldwide, the use of antibiotics in both human medicine and in the production of food from both animals and plants is rising. Antibiotics are today often used uncritically, to treat the wrong things and in the wrong doses. One example from food production is that many countries use antibiotics as growth enhancers. One example from human medicine in Norway is that antibiotics are too often prescriped for upper respiratory tract infections in children, which are generally viral in origin.

In 2013 the amount of antibiotics sold to humans, terrestrial animals and fish in Norway totaled 56.4 tonnes. Humans accounted for 87 per cent, terrestrial animals 11 per cent and aquaculture 2 per cent of the total consumption.

Fig. 1[9]



EXPLANATION - METHENAMINE

Methenamine is classified as an antibacterial medication, but is not strictly an antibiotic. Methenamine breaks down in acidic urine to form formaldehyde, which has a bactericidal effect. Methenamine is used to prevent chronic, recurring urinary tract infections in women. It is used extensively in Norway compared with other countries. Methenamine has a significant impact on the statistics covering pharmaceutical use. It has not been documented that Methenamine drives resistance.

Human health

Around 85 per cent of all antibiotics intended for use in humans are prescribed by general practitioners, while 7-10 per cent is prescribed in hospitals and the remainder in other healthcare institutions, like nursing homes.

The amount of antibiotics used by people in Norway is still relatively low, but has grown steadily in the past decade. Consumption is highest in adult women, around 30 per cent higher than for men in the same age groups. Consumption is also lower in the Northern Norway Regional Health Authority than in the three southern regions. The differences in consumption are due to several factors, such as different prescription practices, different expectations on the part of the public and access to medical services. It is not known which of these factors is of greatest significance.

Antibiotic use has risen marginally from 15.6 DDD 1[10]/1000 inhabitants in 2005 to 15.7 in 2014. Consumption increased in the period 2005-2012, but has fallen again in the past two years.

Consumption of penicillins has doubled from approx. 4 DDD/1000 inhabitants in the mid-1970s to 8.1 in 2014.

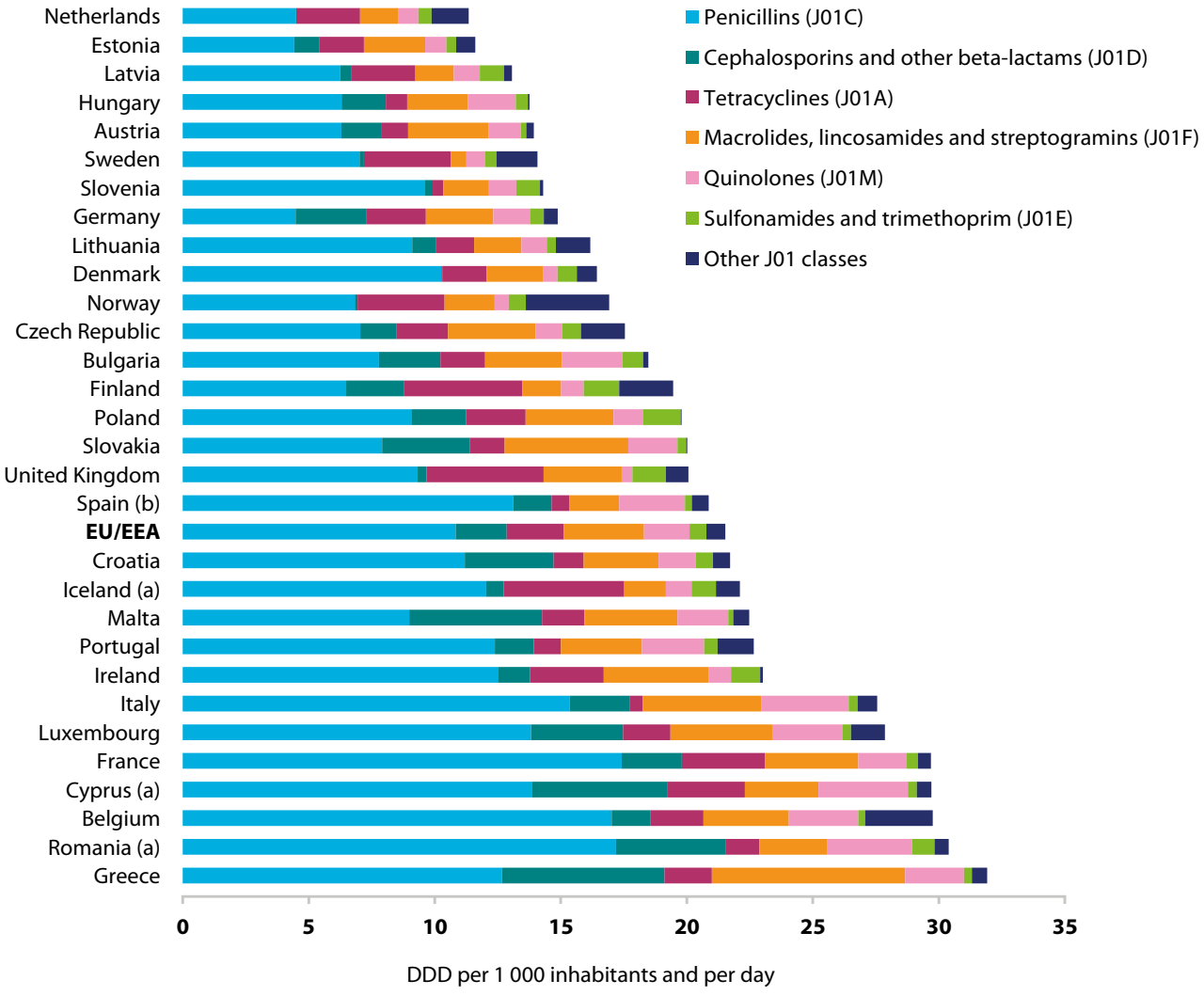
9 Antimicrobial Resistance in Norway. Tromsø / Oslo 2014.

10 DDD = Defined daily doses

Compared with other European countries, Norway is reasonably well placed with regard to the total amount of antibiotics prescribed for human use. Netherless, several naturally comparable European countries have a lower overall consumption of antibiotics without any negative impact on health being documented. This applies particularly to the Netherlands, but also to countries like Sweden, Germany and Estonia. Norway is among the countries that are best placed with regard to prescribing narrow-spectrum rather than broad-spectrum antibiotics.

Fig. 2[15]

Consumption of antibacterials for systemic use (ATC group J01) at ATC group level 3 in the community, EU/EEA countries, 2012, expressed as DDD per 1 000 inhabitants and per day.



(a) Cyprus, Iceland and Romania provided total care data, i.e. including the hospital sector.
(b) Spain provided reimbursement data, i.e. not including consumption without a prescription and other non-reimbursed courses.
EU/EEA refers to the corresponding population-weighted mean consumption.

11 European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2012. Stockholm: ECDC; 2014.

Animal health

Following a downturn in the use of antibiotics for farmed fish in the early 1990s and for terrestrial food-producing animals at the end of the 1990s, the overall consumption by animals has remained relatively stable.

Consumption of antibiotics by Norwegian livestock is among the lowest in Europe. In the period 1995-2013 consumption by terrestrial animals decreased by 35 per cent. For food-producing animals alone, the reduction came to 38 per cent. The most important reasons for our low use of antibiotics is good animal health, skilled and responsible farmers, veterinarians who practice responsible antibiotic use, and close cooperation between the industry and the authorities.

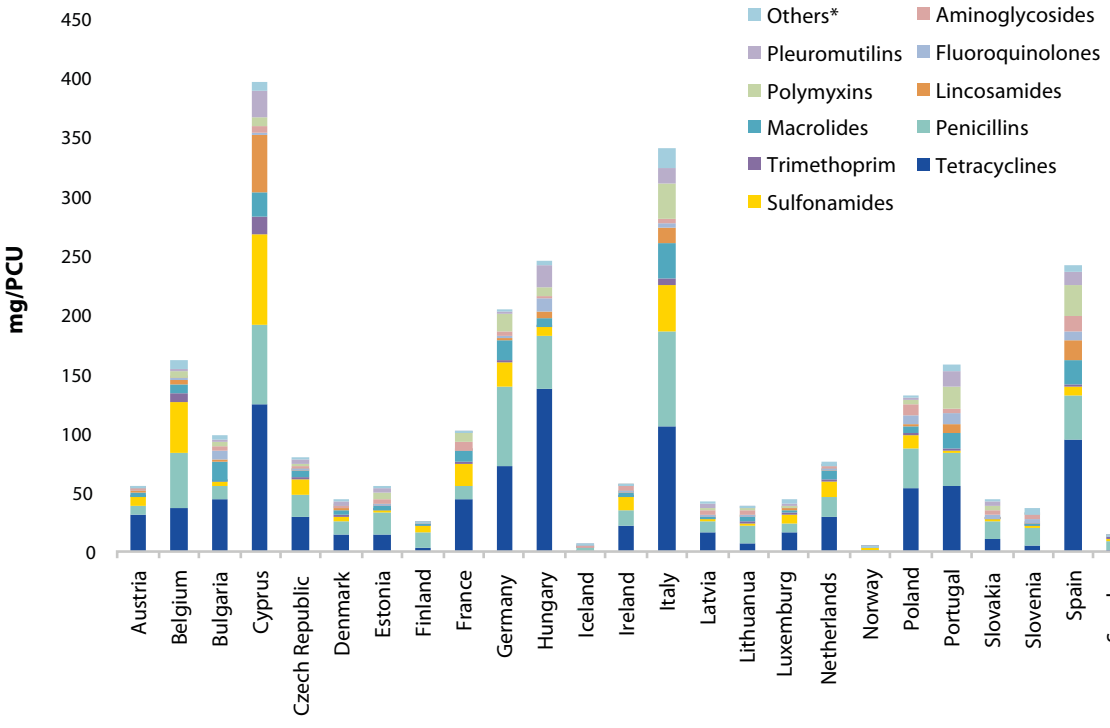
The use of antibiotics in pets rose by 18 per cent in the period 1995-2013. The import (legal and illegal) of pets is substantial, and already represents a risk to both animal and human health. Substantial imports of Eastern European street dogs, in particular, give an increased risk of introducing several diseases that are not found in Norway. These dogs can also be carriers of various resistant bacteria. The NFSA has recently commissioned an opinion from the Scientific Committee on Food Safety with regard to the risk of transferring antibiotic resistant bacteria between pets and people.

The relative consumption of narrow-spectrum penicillin by terrestrial animals doubled in the period 1995-2013, from 25 per cent to 49 per cent of total sales. This is an extremely positive trend because narrow-spectrum antibiotics lead to the development of resistance to a lesser degree than their broad-spectrum counterparts.

Sales of antibacterial medication to the the aquaculture industry totaled 972 kg of active substance in 2013. From the peak year of 1987 to 1996, antibiotic use by the Norwegian aquaculture sector has decreased by 99 per cent. After 1996 consumption has remained more or less at the same level, despite an increase in the production from scarcely 300,000 tonnes in 1996 to 1.2 million tonnes in 2013.

Fig. 3[12]

Sales for food-producing species, including horses, in mg/PCU, of the various veterinary antimicrobial classes, for 26 countries in 2012



12 European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2014. 'Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2012'. (EMA/333921/2014).

EXAMPLE

Large quantities of antibiotics are used in several Asian countries with a long history of freshwater and brackish water fish farming, not only to treat outbreaks of disease, but also as a prophylactic treatment using low doses over a long period. When antibacterial agents are used almost as an operating consumable to compensate for poor environmental conditions, favourable conditions are created not only for the development of resistance in disease-inducing bacteria, but also for the transfer of resistance genes to ordinary bacteria in the environment. With operations integrating both livestock production and aquaculture, human and livestock waste goes straight into the fish pond, and may be the only "nourishment" the fish receive. Under such circumstances, the use of antibiotics by livestock and people could affect both ordinary and disease-inducing bacteria in the aquatic environment, thereby increasing the risk that resistance will develop.

Environment

Bacteria occur naturally in the majority of environments, and in animals and people. A healthy person can have more than a thousand different types of bacteria living on and in their body. The vast majority of these bacteria are useful. Establishment of a bacterial flora in people and animals is due to the ingestion of different microbes through food and water and/or transmission through contact. Both foodstuffs and drinking water can easy be contaminated by illness-inducing bacteria and resistant bacteria from carriers and sick individuals.

Antibiotic resistance is a naturally occurring property in a large number of bacterial species. However, over the past 10-20 years a sharp increase in the occurrence of antibiotic resistant bacteria has been observed in many different ecological niches. There are many reasons for this, but increased antibiotic use, combined with exposure to other resistance-driving substances, such as disinfectants, biocides and heavy metals, probably has major significance. Cosmetics and foods can contain preservatives, but we lack sufficient information about whether this leads to changes in our normal bacterial flora or contributes to the development of resistance.

Studies from India show a higher frequency of resistant bacteria in environments where antibiotic manufacturers dump their waste. However, the knowledge of the consequences for various ecosystems is low regarding other input factors, like fungicides in plant production, as well as the effects of using livestock manure, slurry and water containing antibiotics for fertilization purposes.

EXAMPLE

A survey of the Adriatic found antibiotic resistant bacteria at fish farming sites where antibiotics were used. Data indicate that the aquaculture industry contributes to the spread and maintenance of antibiotic resistance in the marine environment. This may also be the case in Norway, since large quantities of antibiotics were used by Norwegian fish farms up until the early 1990s.

4.3. The burden of disease as a consequence of antibiotic resistance

Burden of disease

A recent report commissioned by the British prime minister estimates that the global mortality rate attributable to antibiotic resistance today is around 700,000 people a year, and that this figure will rise to 10 million in 2050 unless the trend is reversed. In 2007 it was estimated that antibiotic resistance was responsible for 25,000 additional deaths per year in the EU/EEA area. We do not have studies of the burden of disease as a consequence of antibiotic resistance in Norway.

EXAMPLE

Models based on individual studies from various parts of the world show that around 70 per cent of the population in Southeast Asia and 35 per cent of the population in the Middle East carry bacteria with resistant capability extended spectrum beta-lactamase (ESBL) in their intestines.

One study showed that twice as many people die of severe, systemic infection (sepsis) if the infection is caused by a resistant bacterium (ESBL-positive *E. coli*), compared with sepsis caused by a non-resistant strain of *E. coli.*

Financial consequences of antibiotic resistance

In a joint report from 2009, the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) put the additional costs to the health service and loss of productivity due to selected resistant bacteria at approx. EUR 1.5 billion per year in the EU/EEA area.

Sweden has developed a model to calculate the socioeconomic consequences of antibiotic resistance. A preliminary calculation, which has looked merely at the direct costs of medication and treatment in connection with antibiotic resistance in people infected with four reportable bacteria, has estimated a cost of SEK 160 million per year.

In the USA, the President's Council of Advisors on Science and Technology recently estimated that antibiotic resistance leads to 23,000 additional deaths per year, resulting in USD 50 billion in direct costs for the health service and loss of production.

4.4. Ongoing efforts to combat antibiotic resistance

International

A number of parallel initiatives to combat antibiotic resistance are underway internationally. The most important for Norway are:

- In May 2015 the World Health Organization adopted a global action plan against antibiotic resistance13[17] (see panel) in close cooperation with the World Organization for Animal Health (OIE) and the Food and Agriculture Organization (FAO). This will now be implemented. The global action plan stipulates, among other things, that each country should draw up national strategies for efforts in this field
- The FAO passed a resolution against antibiotic resistance in June 2015. The resolution describes how the organization will work, alone and in collaboration with others, to meet the challenges in this area.
- In 2011 the EU launched a transsectoral action plan to combat antibiotic resistance, and a progress report was published in February 2015.

13 http://apps.who.int/gb/ebwha/pdf_filesAVHA68/A68_20-en.pdf

- It has been decided to implement a joint Nordic effort in this area through the Nordic Council of Ministers.

EXPLANATION

The Global Action Plan (GAP) is intended to provide a framework for member states and the WHO to resolve the challenges caused by antibiotic resistance. Although a number of initiatives have been taken after the WHO published its "Global Strategy for Containment of AMR" in 2001, they have led to few tangible measures.

The GAP states that every country should develop national plans for combatting antibiotic resistance. The plan has five strategic goals: 1) increase awareness and understanding of antibiotic resistance, 2) increase knowledge through monitoring and research, 3) reduce incidences of infection, 4) optimize use of antimicrobial agents, and 5) secure sustainable investments in the work to combat antibiotic resistance. Prevention, sustainability and a stepwise approach are the most central of the numerous underlying principles.

In the global context, developing countries are primarily concerned with improving their poor inhabitants' access to effective antibiotics. There are clear expectations that the rich countries should shoulder responsibility for producing new antibiotics. Achieving international agreement on limiting unnecessary use is extremely challenging. One area in which this is evident is the use of antibiotics as growth enhancers in food production. Reserving selected antibiotics for human use in critical situations is another challenge which may prove demanding in the years ahead.

Human health

Monitoring in Norway shows that the problem of resistance is increasing, even though the situation is better than in many other countries. With some infections, such as tuberculosis and gonorrhea, antibiotic resistance is already a major problem. In just a few years, gonorrhea has become an infection that is difficult to treat. Nowadays, most gonorrhea infections are caused by microbes on which antibiotics in tablet form no longer work. The only effective treatment, therefore, is injections with a broad-spectrum antibiotic (ceftriaxon). Although still efficacious, resistance to this preparation is growing.

Of particular concern is the rise in resistance among so-called Gram-negative bacteria, while incidences of methicillin-resistant *Staphylococcus aureus* (MRSA) are growing steadily. In recent years there have also been outbreaks of vancomycin-resistant enterococci (VRE) in hospitals. MRSA is extremely costly for the healthcare sector, due to the need to isolate and treat MRSA-positive patients.

In connection with the national quality indicator system, a national quality indicator group has been set up to devise various quality indicators for antibiotic use and health service-related infections. If all goes according to plan, four quality indicators, which can provide a picture of the use of antibiotics at the municipal level, will be published by the end of 2015.

EXAMPLE

The increasing rate of resistance to carbapenems is particularly serious. These are a group of broad-spectrum betalactam antibiotics, which should, as far as possible, be reserved for the treatment of extremely serious infections in people. Carbapenem-resistant Gram-negative bacteria can now be found worldwide. In the majority of cases, infections caused by carbapenem-resistant bacteria are imported from abroad. However, cases do arise in which importation is not suspected.

Food-producing terrestrial animals and pets

Pigs

In Norway, the first cases of LA-MRSA (livestock-associated methicillin-resistant *Staphylococcus aureus*) were identified in pigs in 2013. This is a bacterium which has little significance for the pig, but which can be transmitted to people, in whom it can, in certain cases, cause extremely serious infections. LA-MRSA is extremely widespread in pig farms in many countries. To obtain an overview of how widespread

the bacterium is in Norwegian pig farms, the NFSA carries out a survey of breeding sow populations numbering more than 10 pigs (around 1,000 herds). The bacterium was found in only one herd of breeding sows, but had been spread onward, through the sale of live animals, to a number of pig herds being raised for slaughter. In the spring of 2015, the NFSA started mapping incidences of the bacterium in herds of pigs being raised for slaughter. Around 950 such herds were examined. In an attempt to prevent the bacteria from establishing a foothold in Norwegian pig production, the affected herds are slaughtered or destroyed, and the farms are cleaned and desinfected. .In those cases we have had in Norway, it seems as though the primary source of the infection has been farm workers infected with LA-MRSA. The bacteria have then spread through the sale of live animals.

Intensified monitoring and effective infection prevention measures, including limited use of antibiotics, is crucial to prevent the spread of such bacteria. It is important that the industry follows the advice given with respect to protection from infection, has appropriate routines for the sale of live animals, and works continuously to reduce the risk of introducing and spreading this kind of infection. Furthermore, it is important that foreign farm workers, pig farmers and others who may be infected are tested for LA-MRSA before they come into contact with a herd of pigs.

Poultry

E.coli that were resistant to broad-spectrum beta-lactam antibiotics (ESBL) were found in Norwegian poultry for the first time in 2006. Such bacteria can be passed between animals and humans, and have also been identified in Norwegian patients. This is one of several potential sources of infection in people. This type of bacteria are often difficult to treat with antibiotics. Since very little antibiotics are used in the production of chickens for slaughter, it is assumed that the resistant bacteria have been imported along with breeding stock. The bacteria has become established in Norwegian poultry flocks, and has also been found in poultry meat.

The poultry industry imports over 90 per cent of its breeding stock from one supplier in Scotland. In 2013 the poultry industry demanded that the supplier cease treating the broodstocks prophylactically with antibiotics. The supplier accepted this demand, and no resistance was identified in imported breeding stock in 2014. The industry has implemented a number of measures to reduce the incidence of resistant bacteria in Norwegian poultry flocks. This has resulted in a reduction in the presence of resistant bacteria in parent birds, from 30 per cent in 2011 to 10 per cent in 2014.

A relatively high incidence of Quinolone-resistant *E.coli* in poultry birds and meat has also been found. In 2013 a new method found Quinolone-resistant *E.coli* in almost 50 per cent of the turkey fillets examined. Preliminary results from the monitoring undertaken in 2014 indicate that the incidence is also high in chickens and chicken fillets. Historical data from the surveillance program indicates that the incidence of this type of resistance has remained at the same level since the first surveys were undertaken in 2000. It is also known from other countries that the incidence of Quinolone-resistant *E.coli* can be high in poultry. As a rule, Quinolone-resistant *E.coli* do not cause illness in animals. The bacteria are part of the natural microbial flora in the intestines. However, the bacteria can be passed to people. Quinolones are considered critically important antibacterial agents, which should – preferably – only be used for the treatment of serious infections in people. Quinolone is not administered to poultry in Norway, and it is not known why the incidence rate is so high.

With the help of research grants under the Agricultural Agreement, as well as funds from the Foundation for Research Levy on Agricultural Products (FFL) and the industry itself, a competence project has been established to investigate Quinolone resistance.

EXAMPLE

The animal feed additive narasin is routinely given to poultry destined for the table to prevent the infection coccidiosis. It has not been documented that narasin is significant with respect to the antibiotic resistance identified in Norwegian chickens. Nor, according the Norwegian Institute of Public Health, has narasin use in poultry been documented as having any negative effects on human health. Nevertheless, certain studies indicate that use of narasin may be of significance for the development of antibiotic resistance. This uncertainty means that both the public authorities and the industry itself wish to find good alternatives to the use of narasin.

Cattle

Through the NORM-Vet program, samples have regularly been taken to test certain bacteria (indicator bacteria) in the normal intestinal flora of cattle for antibiotic resistance. Occasionally, illness-inducing bacteria from cattle are also analyzed in connection with NORM-VET. Intestinal bacteria showing resistance to certain antibiotics have been found in only a few cases. These finds probably have little significance for animal and human health. In this year's program, samples will also be taken of cattle with respect to ESBL and MRSA. The results of these surveys are not yet available.

Sheep

Bacteria from sheep have also been tested by NORM-VET. In the same way as for cattle, intestinal bacteria showing resistance to certain antibiotics have been found in only a few cases, and the finds probably have little significance for animal and human health.

Pets

Multiresistant bacteria are increasingly often found in dogs and cats. For example, ESBL and an extremely resistant Staphylococcus bacterium, akin to *Staphylococcus aureus* in humans, has been found in dogs. As far as possible, animals should not be given antibiotics that are critical to the treatment of infections in humans[14].

14 This is important for all animals, not only pets.

Fish

In 2013 only 1 per cent of farmed fish in Norway received one single treatment with antibiotics. This has been achieved after intensive research, including research in the field of vaccines. Despite this, the farming of new species may cause problems with infections we do not have vaccines for. Vaccines for new species, such as cleaner fish, should continuously be developed. At the same time, more effective vaccines should also be developed against viral diseases, which can, in turn, make the fish more susceptible to bacterial infections.

The development and use of effective vaccines has been, and still is, the most important strategy to avoid the need for antibiotics in fish farming. Other important factors include breeding for increased resistance to disease, better operating routines to produce more robust stocks, stricter standards for water circulation at fish farms and improved hygiene for infection prevention and control.

EXAMPLE

Studies of Norwegian fish farming have been undertaken to examine the development of antibiotic resistance in both pathogenic bacteria and in environmental sediments.

Vibrio salmonicida, which causes cold-water vibriosis particularly in salmon, was a major problem in the late 1980s. After more than six seasons of frequent treatments with oxytetracyclines, resistance to oxytetracylines was found along large parts of the Norwegian coast within a few months. This was despite the standard practice of fish health personnel in Norway not to initiate antibiotic treatment until a diagnosis had been made and a resistance test carried out. Detailed studies of *Vibrio salmonicida* and possible resistance genes are still underway, but the results of these investigations will not be published for several years.

Food

There has been a lot of media coverage of antibiotic resistant bacteria in Norwegian poultry and pork meat, particularly in the past couple of years. According to the NFSA and the public health authorities, good hand

and kitchen hygiene will protect us against antibiotic resistant bacteria. There is no risk of contracting an infection from eating meat, as long as it is sufficiently well cooked. Nevertheless, the presence of antibiotic resistant bacteria is unwanted, and we do not have any guarantee that everyone follows the hygiene advice. Antibiotic resistant bacteria could also be spread via foods that are not normally cooked before they are eaten, e.g. fresh vegetables used in salads.

Environment

Bacteria populations in nature (soil, water, sediments) can be exposed to other microbes and/or DNA from the manmade environment. Such exposure creates opportunities for the exchange of genetic material. It was previously assumed that the spread of resistance genes occurs largely from manmade environments to natural environments. More recent studies, however, indicate that bacteria in nature may also be a source of resistance, which is spread to illness-inducing bacteria in clinical environments. There is a general lack of knowledge about how and to what extent this happens. Colonies of bacteria in, for example, the soil, fresh water, seawater and sediments, as well as organisms associated with these environments, have not been sufficiently well studied.

There is also limited knowledge about the presence of antimicrobial agents and disinfectants in the Norwegian natural environment. More recent studies indicate that antibiotics, even in extremely low concentrations, can lead to the development of resistant bacteria. The presence of antibiotics in low concentrations can be expected in environments exposed to sewage and runoffs from livestock farming/fertilizer and from sources where antibiotics are used in human and veterinary medicine.

If genetically modified plants, which have received marker genes for antibiotic resistance are introduced into the natural environment, the subsequent transfer of antibiotic resistance genes from these plants to bacteria via so-called horizontal gene transfer cannot be excluded. Although the probability of any such gene transfer is low, the consequences would nevertheless be serious if the resistance properties were to find their way into illness-inducing bacteria. For this reason, Norway has so far pursued a restrictive policy, emphasizing the precautionary principle in its assessment of genetically modified organisms with antibiotic resistance genes. Genetically modified products intended for human and animal consumption and containing antibiotic resistance genes are banned under the Norwegian Food Act.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