

IMPROVING THE EFFECTIVENESS OF ANTIBIOTICS, CURBING RESISTANCE

Summary and recommendations
of the National Research Programme
“Antimicrobial Resistance”

Contents

Foreword	3
Key results and recommendations of NRP 72	5
Background and basis of this report	9
1 Background: antibiotic resistance is increasing, yet the countermeasures to date are not adequate	11
2 The prerequisite for effective measures: know what's happening	23
3 Curbing the emergence of resistance: prevention and optimised use of antibiotics	33
4 Overcoming existing types of resistance: new antibiotics	46
Overview of research projects NRP 72	55
Publication details	56

Foreword

When we embarked on the research work for NRP 72 in 2017, I was aware of the major threat posed by increasing antibiotic resistance. But I would never have thought that just three years later, the Covid pandemic would give us first-hand experience of the far-reaching effects that a single infectious disease can have, against which there are no effective medicines. Since all bacterial pathogens are becoming resistant to antibiotics, we may potentially find ourselves dealing with several pandemics at the same time. If the current trend continues unabated, we will be confronted by grave consequences in just a few years' time. This is because antibiotics are a linchpin of modern medicine. They cure infections that would otherwise prove extremely serious or fatal. Furthermore, they prevent infections in just about every operation, in cancer treatment and in countless other applications. If resistance vanquishes their efficacy, we will lose one of the greatest medical achievements ever.

But it doesn't have to come to that. On the contrary, after five years of research under the auspices of NRP 72, I am cautiously optimistic. Optimistic because we can in fact do something. Science shows how we can reduce and improve antibiotic use, how we can monitor outbreaks of resistant pathogens more effectively and contain them at an early stage, and how we can improve the way we diagnose and treat these infections. However, we need to be clear about the fact that the issue of resistance will continue to worsen. And it will not be sufficient to – in Switzerland at least – further optimise the way antibiotics are used. We also need new antibiotics capable of overcoming existing and emerging resistances. Sadly, this is an area where there is little cause for optimism. Although the research – including research done for NRP 72 – regularly produces good results, these do not make the transition to real-world use. The problem is not a scientific one, but an economic one. Developing new antibiotics does not seem to be financially worthwhile.

- 3 So while I am confident that many of the results from NRP 72 will promptly be put into actual use, I would like to emphasise that Switzerland in particular needs to shift up a gear when it comes to the development of new antibiotics. This is because it is a world leader in pharmaceutical innovation, and that brings certain obligations with it. However, it also brings opportunities and might prove to be a

fruitful investment for the future. The same applies to all the action areas for which NRP 72 has identified solutions. If we are proactive in taking action now, we will not only avoid a potentially full-scale crisis, we will also strengthen all the sectors involved, from healthcare provision and animal production to the pharmaceutical industry. Researchers working on NRP 72 have supplied much of the groundwork for this, and I would like to express my sincere gratitude to them all.

Joachim Frey

President, NRP 72 Steering Committee

Key results and recommendations of NRP 72

New findings and instruments for practitioners

The National Research Programme “Antimicrobial Resistance” (NRP 72) has produced an abundance of new findings and instruments. Many of them will make it possible to take rapid, targeted action. This applies to measures that could minimise the spread of antibiotic resistance at important interfaces as well as to those that have been proven to reduce and improve antibiotic use. Other measures require longer-term planning involving various players. Not least among these is the establishment of an antibiotic resistance monitoring system based on genetic data of bacterial pathogens and recording these together across humans, animals and the environment.

Many of the measures can be implemented within the framework of the existing federal strategy

Many of the measures, whether new diagnostic methods or prevention-driven operational processes, directly address the practices of individual institutions and professionals, for example in animal production, human and veterinary medicine or GP practices. However, shared-interest associations and specialist organisations play an important role in establishing new standards, and it is the task of the government and authorities to create the necessary framework conditions and obligations for this to happen. The cantonal health and agriculture departments are particularly important in this context. At national level, the antibiotic resistance strategy (StAR) provides a suitable framework within which the Confederation can initiate implementation of these measures and coordinate the relevant key players.

Call for decisive action on antibiotic development

Research conducted for NRP 72 delivered highly promising approaches for novel innovative antibiotics. Unfortunately, the antibiotics market is not profitable at present, and there is a shortage of industrial partners willing to build on academic research by financing the expensive task of developing usable medicines. This market failure cannot be resolved by scientific innovations. Instead, it is a challenge for government, which must create new framework conditions so that the financial risks associated with drug development are attractive again for new antibiotics. This is an area where Switzerland, as a leader in pharmaceuticals and biotechnology, has the capacity to take a pioneering role and act decisively.

Results and recommendations in three action areas

1 Knowing what's happening – the key to effective action

With the aid of gene sequencing technologies, researchers working on NRP 72 discovered important interfaces and links in the processes by which antibiotic resistance spreads. These include the transmission of problematic multi-resistant pathogens from animals to the staff of veterinary clinics or detecting elevated concentrations of resistance genes in rivers downstream from sewage treatment plants. Many of these findings make it possible to take specific action to stop the spread of antibiotic resistance.

The new technology of whole genome sequencing in particular promises more. By linking genetic data concerning resistant pathogens from human and veterinary medicine and the environment, it should be possible to trace in detail the transmission paths of antibiotic resistance across all these areas. Researchers working on one NRP 72 project developed a database for this purpose. The Swiss Pathogen Surveillance Platform (SPSP) provides the basis for surveillance of antibiotic resistance, which is far more comprehensive than any to date.

NRP 72 recommends

- taking action to break transmission chains at the antibiotic resistance transmission interfaces identified by NRP 72;
- augmenting antibiotic resistance monitoring in all areas (humans, animals and the environment) with whole genome sequencing data, and jointly analysing these data.

2 Slowing the development and spread of resistance – optimised use of antibiotics

Researchers working on NRP 72 have developed tools and interventions to support professionals when they prescribe antibiotics. For example, the new online AntibioticScout tool has already become an established part of veterinary practice. Also, a new approach to calf fattening is producing impressive results: by adopting prevention measures, the “outdoor veal calf” system avoids infections and reduces antibiotic use by around 80 per cent.

Real-world studies in human medicine show that suitable interventions result in more targeted use of antibiotics. Several success factors were identified. Of these, antibiotic prescription monitoring is key. However, no monitoring system exists as yet in the primary care setting. In one project, researchers developed a method of monitoring prescription using data that is routinely collected anyway. And in one study, a new diagnostic procedure resulted in GPs prescribing antibiotics for respiratory tract infections about a third less often.

Since rapid and accurate diagnosis is a key element of good antibiotic prescribing habits, several NRP 72 projects researched completely new tests that supply results faster than conventional methods. Some of them are already being used in practice. While others still have some way to go before they reach this stage, they nevertheless prove that diagnosis can in principle be speeded up hugely.

NRP 72 recommends

- systematically pursuing the current federal-level efforts to improve animal welfare and health, and, within these efforts, focusing more on preventing infection in animal facilities;
- constantly refining veterinary treatment guidelines and incorporating them in the AntibioticScout online tool;
- implementing long-term antibiotic stewardship programmes in hospitals according to criteria defined by the National Center for Infection Control (Swissnoso) and taking account of new insights from NRP 72;
- developing a national strategy to promote good antibiotic prescribing habits in human primary care;
- accelerating approval procedures for new diagnostics and adequately reimbursing their use in practice.

3 Overcoming existing resistances – new antibiotics

NRP 72 researchers have discovered and generated a range of new antibiotic active substances capable of overcoming existing resistances. These include as yet unknown substances from the natural environment as well as synthetic substances. Furthermore, some projects have yielded new methods for systematically searching for further active substances.

Despite the highly promising and internationally acclaimed work performed in the context of NRP 72, the results from only one project have as yet made their way into clinical drug development. The pharmaceutical sector's lack of interest in novel antibiotics is due to the low prices of antibiotics. In addition, innovative antibiotics are earmarked as reserve medicines that are used as little as possible, which limits sales volumes. For these economic reasons, most large pharmaceutical companies and investors have withdrawn from this area.

NRP 72 recommends

- providing new economic incentives that make it worthwhile for industry to maintain long-term, diversified antibiotics programmes;
- taking an active role in international initiatives that ensure the development of and access to new antibiotics;
- securing funding for excellent basic research and clinical development of antimicrobials in Switzerland.

Background and basis of this report

NRP 72: a comprehensive research programme on antibiotic resistance

Antibiotic resistance is a growing problem. This is why the Federal Council mandated the Swiss National Science Foundation to launch the National Research Programme “Antimicrobial Resistance” (NRP 72) in 2015. It was planned in coordination with the Swiss Antibiotic Resistance Strategy (StAR).

For NRP 72, scientists spent five years researching new approaches in 33 projects at Swiss universities and higher education institutions, as well as in 12 international projects as part of the European Joint Programming Initiative on Antimicrobial Resistance (JPIAMR). Their aim is to contribute to

- curbing the spread of antibiotic-resistant pathogens;
- using antibiotics more responsibly;
- improving the treatment of infections with antibiotic-resistant pathogens.

Analyses and recommendations in three thematic synthesis reports

NRP 72 researchers have jointly analysed their results and discussed them with representatives of numerous national and international bodies of practitioners and policymakers in respect of the three principal aims of the programme. Three thematic synthesis reports have emerged from these processes.

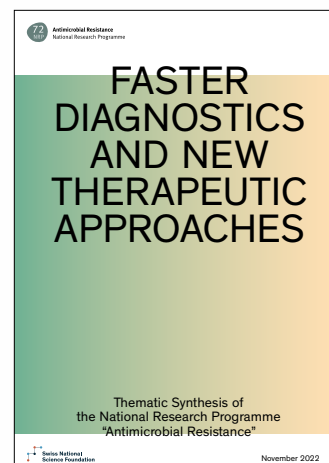
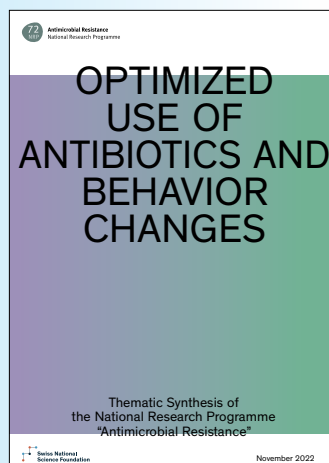
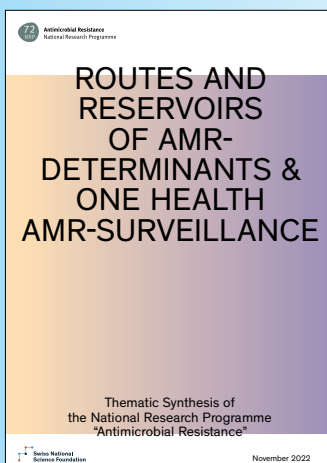
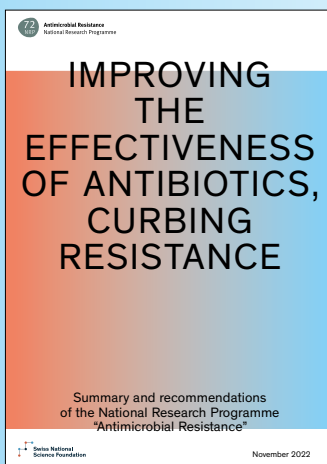
The three reports – each drawn up by a working group consisting of NRP 72 researchers – explain the background to the various themes, appraise new findings from NRP 72 and formulate practice-oriented recommendations for action. They are presented in English and are addressed to experts and to anyone with an interest in science.

- *Routes and reservoirs of AMR-determinants & One Health AMR-surveillance*
- *Optimised use of antibiotics and behaviour changes*
- *Faster diagnostics and new therapeutic approaches*

Programme summary of NRP 72: a strategic orientation

The three thematic synthesis reports, together with the results of individual research projects, form the most important basis for the present programme summary. This summary is aimed not only at decision makers in the fields of practice and policy, but also the general public. In it, the Steering Committee summarises the key background information, action areas and measures that, in its view, emerge from the work of NRP 72.

All background information and results for NRP 72 can be found at www.nrp72.ch



1

Background:
antibiotic resistance
is increasing,
yet the countermeasures
to date are not adequate

Antibiotics are one of the central pillars of modern medicine

Antibiotics act against infections caused by bacteria. They are some of the most commonly used medications, in both human and veterinary medicine. Their wide availability since the mid-1940s has significantly increased average life expectancy in much of the world, because many serious infectious diseases – the most common cause of death before the antibiotic era – can now be cured. These diseases include tuberculosis, syphilis, typhus and pneumonia, as well as blood poisoning from even minor wounds.

Today, antibiotics are used in almost all areas of medicine. In Switzerland, one person in five receives antibiotics in any given year, as do half of all hospital inpatients. As well as being used to treat infections in primary care, antibiotics have also become indispensable in numerous specialist areas, ranging from the majority of surgical interventions through to cancer therapies (see illustration on next page).

Depending on the area of application and the pathogen involved, various antibiotics may be used: broad-spectrum antibiotics are active against many different pathogens, while narrow-spectrum antibiotics target specific groups of bacteria. There are currently 14 classes of antibiotic, which differ in the way they act. Some antibiotics kill bacteria directly while others prevent them from multiplying, thus bringing an infection to a halt.

Antibiotics in human medicine

Antibiotics can be used to treat bacterial infections such as septicaemia, cystitis, pneumonia and tick-borne Lyme disease. They are also indispensable as prophylactics in numerous areas of medicine, from surgical interventions such as organ transplants or heart operations through to oncological chemotherapy and dental surgery.



Antibiotic resistance is threatening the effectiveness of antibiotics

The immense benefits of antibiotics for individual and public health are, however, under threat. They are being jeopardised by antibiotic resistance, which occurs because bacteria can stop responding to antibiotics. Infections with antibiotic-resistant pathogens are difficult – and increasingly even impossible – to treat.

In principle, bacteria become resistant to certain antibiotics randomly. When they undergo genetic change, this in turn leads to some of their components (e.g. proteins) also changing or even completely disappearing. If this affects the exact sites that a particular antibiotic needs to target, it will become ineffective.

These types of genetic changes can arise in two different ways:

- Through mutation: In order to multiply, bacteria replicate their own genome. Errors often occur during this process. The next generation of bacteria then exhibits slightly different characteristics. This sometimes makes them resistant to antibiotics.
- Through horizontal gene transfer: Bacteria have the ability to transfer mobile genetic elements to each other and incorporate them in their genomes. New genetic characteristics are thus passed between bacteria, sometimes leading to resistance to a particular antibiotic.

Even if only a few individual bacteria develop resistance at first, entire bacterial populations can very rapidly become resistant to antibiotics. This is because when a bacterial population comes into contact with an antibiotic, only the resistant bacteria survive. In the absence of competition, they can then multiply unhindered, and their genetic material spreads throughout the population.

This process, known as selection, has been occurring naturally for millions of years. Many microorganisms produce substances with an antibiotic effect, in order to defend themselves against bacterial enemies. However, when antibiotics are used as medicines, the process is faster: the more frequently bacteria are exposed to antibiotics, the more often selection occurs, and the greater the number of bacteria that become resistant to these particular antibiotics.

Antibiotic resistance is spreading globally – between human beings, animals and the environment

Pathogens can become resistant to antibiotics used in both human and veterinary medicine. Once antibiotic resistance has arisen, it can spread throughout the entire human-animal-environment biological system. This is because many species of bacteria colonise both people and animals. Furthermore, horizontal gene transfer can enable bacteria to transfer the genetic causes of antibiotic resistance, i.e. individual resistance genes, to other species of bacteria.

This leads to diverse transmission chains, potentially involving numerous bacterial species across different ecosystems. In addition, the complex transmission routes of antibiotic resistance have assumed an increasingly global dimension in recent decades, as international trade and passenger travel help antibiotic resistance spread throughout the world much faster than before.

It is therefore becoming widely recognised that curbing the problem of resistance calls for an approach addressing the fact that human and animal health are closely linked to each other and to the environment. This is known as the One Health approach.

The spread of antibiotic resistance

Antibiotic-resistant pathogens and antibiotic-resistance genes spread via human beings, animals and the environment, locally and globally. This close connection between the health of people and animals is therefore referred to as “One Health”.



Antibiotic resistance and the deaths and complications it causes are increasing worldwide

Antibiotic resistance has been growing throughout the world for many years. However, there are no precise figures on the global situation, since there is no systematic monitoring in large parts of the world. This can be a particular problem in countries and regions considered to be hotspots for the emergence and spread of new types of resistance, including South Asia and parts of South America. These regions are seeing the appearance of more and more pathogens that are resistant to several or even all available antibiotics; they are known as multi-resistant pathogens.

It has been calculated that over 1.25 million deaths were directly caused by antibiotic-resistant bacteria in 2019. The situation is alarming even in regions with comparatively low figures: in Western Europe, over 51,000 people died of infections caused by resistant pathogens in 2019. In a significantly higher number of cases, these lead to serious complications and poorer outcomes rather than actual death.¹

All the forecasts predict that these figures will go on rising. Experts agree that if the current trend continues, infectious diseases will once again become one of the leading causes of death throughout the world by the middle of the century, with several million deaths annually. This is likely to have far-reaching consequences in other areas of society, with enormous costs resulting from additional health spending and lower productivity.

In the first instance, concern about the dwindling efficacy of antibiotics relates to human medicine and human health. Yet animals, and particularly livestock, are increasingly being affected by antibiotic-resistant germs, which are jeopardising animal welfare throughout the world. The regional hotspots are very much the same as those where antibiotic resistance is having an important impact on human medicine.²

Deaths and complications are rising in Switzerland too

By international standards, Switzerland is not greatly affected by antibiotic resistance. Nevertheless, related deaths in this country rose from about 150 to nearly 300 a year in the decade from 2010 to 2019. During the same period, the total number of infections with antibiotic-resistant pathogens requiring special medical care rose from 3000 to over 6000 annually.³

However, it is not the case that all types of antibiotic resistance to every pathogen is increasing (see page 17). Systematic monitoring of selected pathogens was introduced in Switzerland in 2004, and this reveals differing trends: specific types of resistance to certain pathogens have increased strongly, while the situation with other pathogens and types of resistance has remained stable or even improved slightly.⁴

The picture is much the same for livestock, although in some cases resistance rates are at a significantly higher level. Different trends can nevertheless be observed here too, depending firstly on the type of pathogen and resistance, and secondly on the species of animal (see page 18).

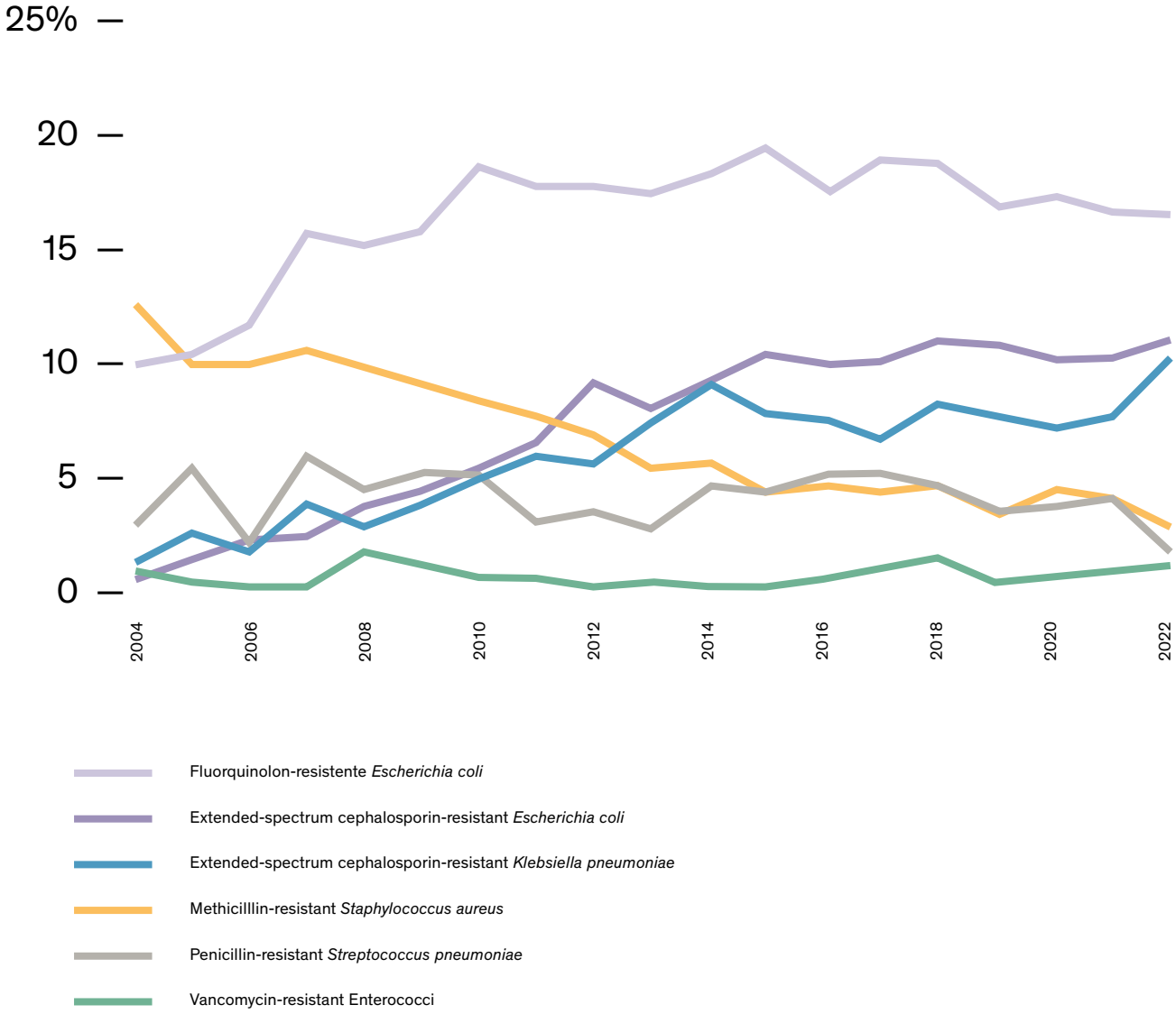
¹ Murray CJL et al.: Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* (2022)

² Van Boeckel TP et al.: Global trends in antimicrobial resistance in animals in low- and middle-income countries. *Science* (2019)

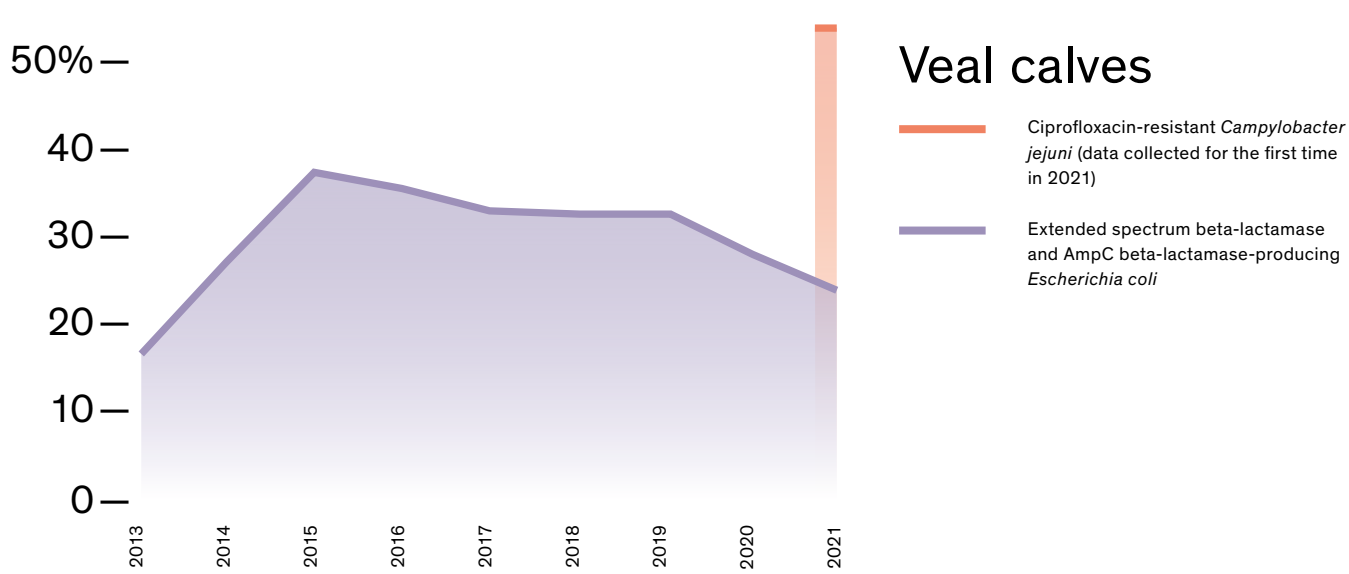
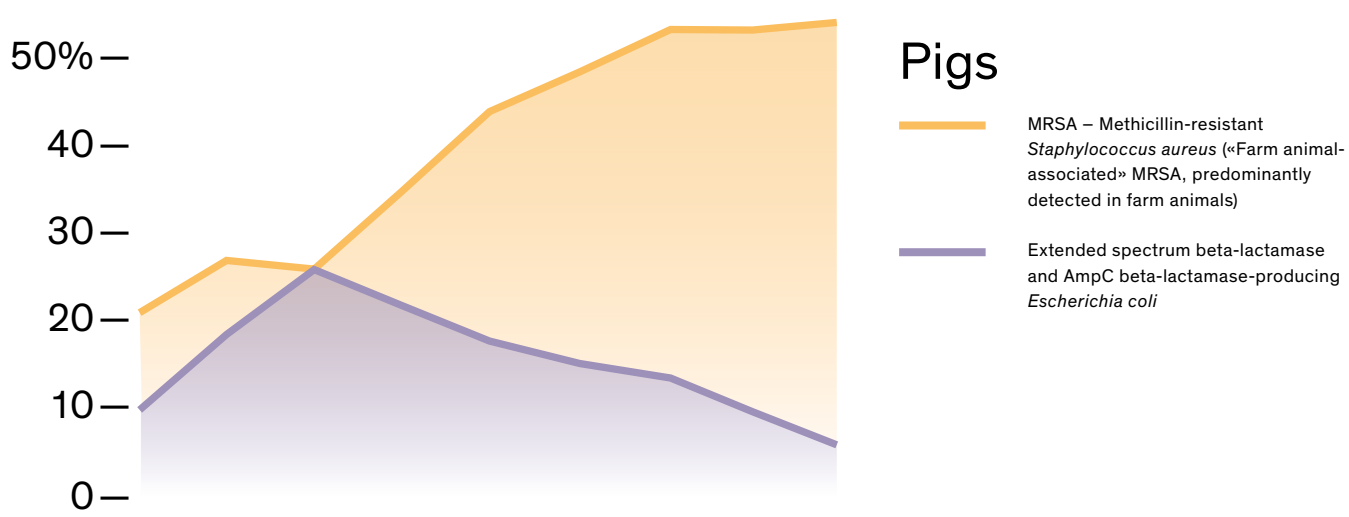
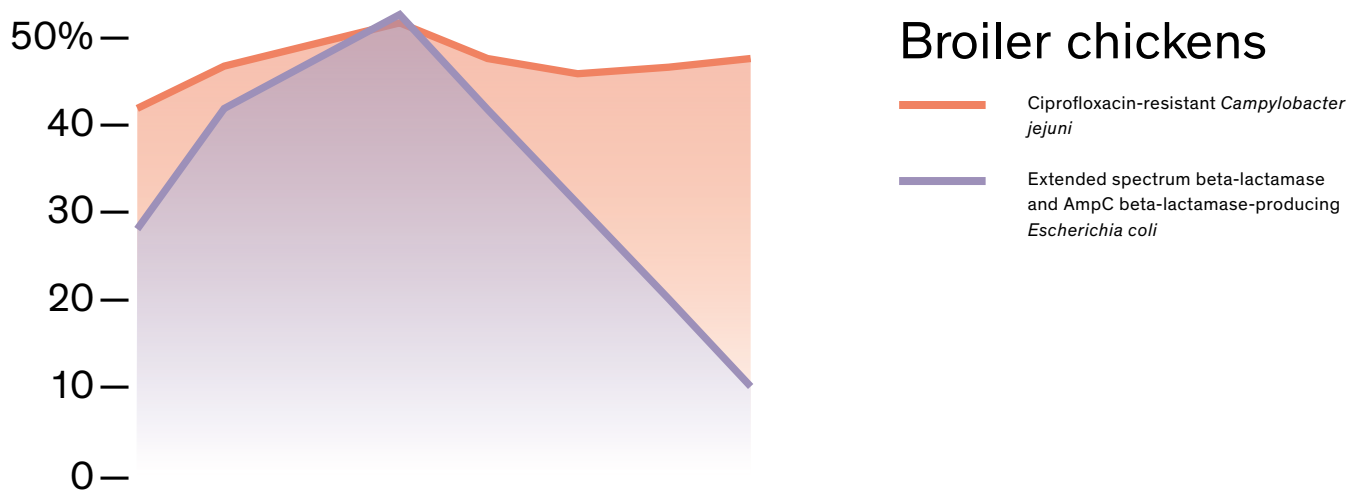
³ Gasser M, Kronenberg A, and the Swiss Centre for Antibiotic Resistance (ANRESIS): Attributable deaths and disability-adjusted life-years (DALYs) caused by infections with antibiotic-resistant bacteria in Switzerland from 2010 to 2019. ECCMID – European Congress of Clinical Microbiology and Infectious Diseases, online (2021)

⁴ Federal Office of Public Health (FOPH): Swiss Antibiotic Resistance Report 2022. BAG (2022)

Resistance in humans in Switzerland



Resistance in farm animals in Switzerland



The problem is being driven by improper use of antibiotics and by global interconnectivity

When antibiotics are used unnecessarily or incorrectly in human or veterinary medicine, this favours the emergence of antibiotic resistance. The same applies to the use of antibiotics for non-medical purposes, for instance as growth promoters in livestock farming (banned in Switzerland since 1999). This is because while a suboptimal dosage often kills a large number of bacteria, it does not kill those that already have some resistance. When this process keeps being repeated, it steadily drives the selection of the most resistant strains of bacteria. Nowadays, once resistance to an antibiotic has developed, it can spread regionally and globally through international trade and passenger travel.

Antibiotic usage soaring worldwide

In the past 20 years alone, the use of antibiotics in human medicine has increased by about 50% worldwide.⁵ The biggest rise is in countries where access to antibiotics has been made easier. Meanwhile, the quantity of antibiotics used in livestock production has also gone up significantly. This trend is expected to continue. It is principally attributable to more intensive meat production and consumption in emerging countries such as India, Brazil, China and Russia. By contrast, most European countries have been able to reduce antibiotic use in livestock farming in recent years.

Antibiotic consumption in Switzerland: stable to slightly decreasing in human medicine, decreasing in animal production

The consumption of antibiotics in hospitals has remained stable in Switzerland in recent years, and has fallen slightly in outpatient care. It is on the low side by European standards.

In livestock farming, the total quantity of antibiotics sold has been declining appreciably for a number of years. This also applies to classes of antibiotics that are of critical importance in human medicine and should therefore not be used in veterinary medicine if at all possible, in order to prevent the emergence of resistance to these important medications. As with the development of resistance, however, trends in antibiotic use vary for different antibiotics and animal species.

⁵ Browne AJ et al.: Global antibiotic consumption and usage in humans, 2000–18: a spatial modelling study. *Lancet* (2021)

Few new antibiotics are being developed – in spite of urgent need

An increasing number of infections with multi-resistant pathogens are now very difficult or even impossible to treat. There is therefore a global need for new antibiotics that can overcome the existing forms of antibiotic resistance. However, hardly any such medicines have been developed for years now. In fact most of the antibiotics currently used in medicine date back to the “Golden Age of antibiotic development” between 1940 and 1960.

According to the WHO, work on developing new antibiotics is currently far from satisfactory. Indeed, almost all the big pharmaceutical companies have abandoned their antibiotic research by now. The reason for this is simple: antibiotics make little or even no money. They are generally administered for only a short time during medical treatment and they are priced very cheaply. Furthermore, novel antibiotics can only be used in a limited way right from the start, since they count as reserve antibiotics which need to keep on working for as long as possible so that they can treat cases where resistance has caused all other medications to fail.

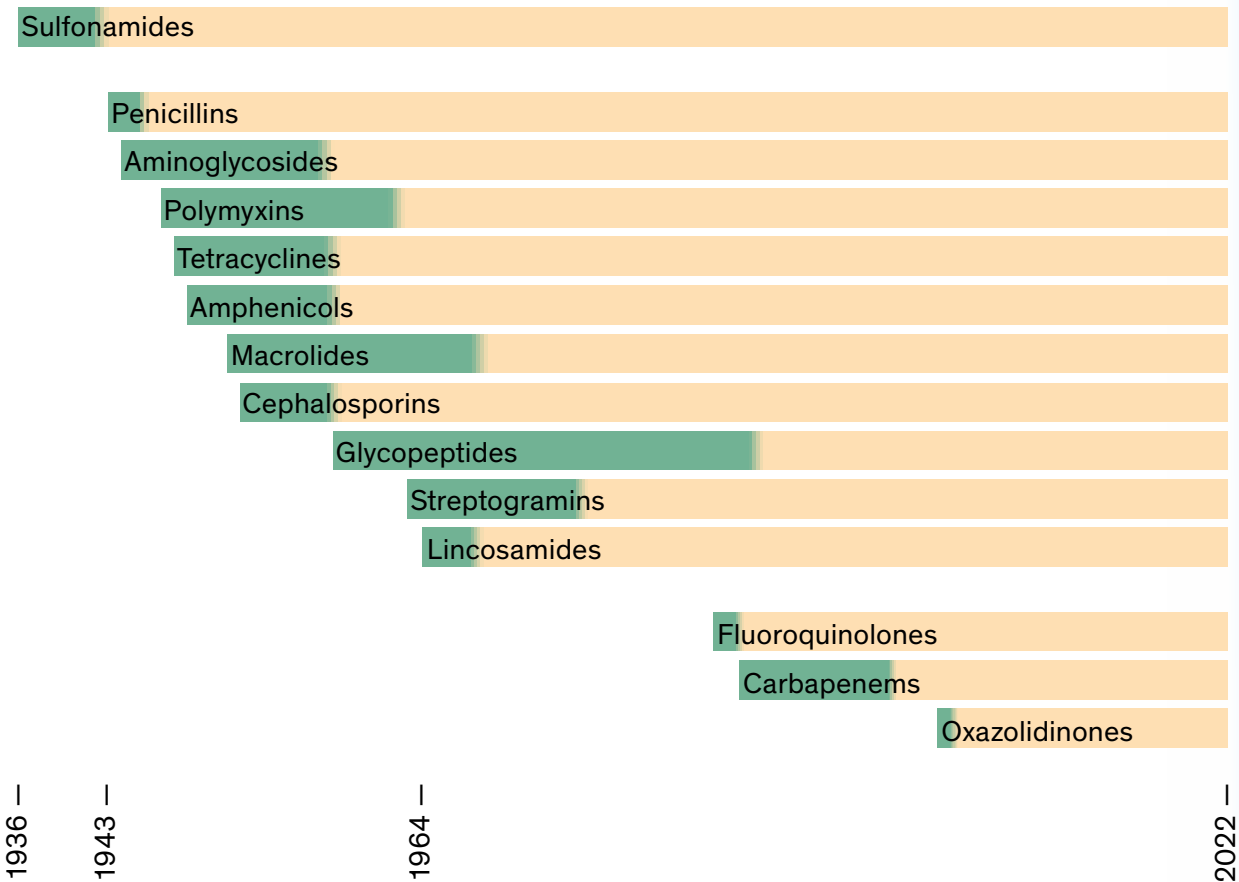
In 2021, fewer than 30 antibiotic agents that might be effective against major resistant pathogens were actually in clinical development anywhere in the world.⁶ Meanwhile, over 6000 financially far more attractive oncological substances were in development in the same year.⁷

⁶ WHO: 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis. WHO (2022)

⁷ Mark Ratner: Oncology Market Trends: Predictive Biomarkers, New IO Targets And Tougher Competition. At [invivo.pharmaintelligence.informa.com](https://www.invivopharmaintelligence.informa.com), online (2022)

Market launch of the most important classes of antibiotics

Most of the classes of antibiotics in use today were discovered and introduced as medicines between 1940 and 1960. Antibiotic resistance has developed against all of them (indicated by the colour change in the graph). There is therefore a great need for new antibiotics, yet hardly any have come onto the market since the 1970s.



Interim conclusion: the problem is growing, and measures to date have not stopped the trend

Antibiotic resistance has become a public health issue throughout the world. By international standards, however, Switzerland is not yet greatly affected: the individual risk of treatment failure owing to resistant pathogens is small, and the healthcare system is not severely threatened. Nevertheless, the trend in Switzerland and worldwide make one thing absolutely clear: the problem is steadily worsening.

The World Health Organization (WHO) has recognised the threat posed by antibiotic resistance and in 2014 it launched a global action plan. Many countries have introduced measures in line with this framework. The One Health approach is a central pillar of most of these national and international programmes. It is also the basis of the Swiss Antibiotic Resistance Strategy (StAR) launched by the Confederation in 2015, under which several federal agencies coordinate extensive efforts in the areas of human and veterinary medicine, agriculture and the environment.

However, the relentless global trends in antibiotic resistance, antibiotic usage and the supply of new medications indicate that the measures introduced so far are not enough.

2

The prerequisite for effective
measures:
know what's happening

Monitoring antibiotic resistance and antibiotic usage is the basis for action

Targeted measures against the spread of antibiotic resistance must be based on knowledge of what is actually happening. It is important to have up-to-date data on the emergence of resistant bacteria, as well as on the use of antibiotics. This forms the basis for

- Recognising and curbing outbreaks involving resistant pathogens in individual institutions (e.g. hospitals), as well as at regional and global level.
- Constantly adapting clinical practice as regards diagnosis and treatment to the current situation. This benefits patients while reducing the emergence of new types of resistance.
- Targeting the development of new treatments specifically at antibiotic-resistant pathogens that are significant for public health.
- Making medium- to long-term decisions on national policy based on the evidence.
- Testing the effectiveness of the measures undertaken.

More and more countries and international organisations are therefore systematically gathering data on antibiotic resistance and usage. The most important international monitoring networks include the Global Antimicrobial Resistance and Use Surveillance System (GLASS) run by the WHO and the European Antimicrobial Resistance Surveillance Network (EARS-Net) run by the EU. Both gather data from participating countries and amalgamate it to obtain an overview. Switzerland, too, supplies data to these networks.

Monitoring in Switzerland is good, but there are still gaps

In Switzerland it is the Swiss Centre for Antibiotic Resistance (ANRESIS) which documents and analyses reports of antibiotic-resistant pathogens in human medicine as well as the use of antibiotics in hospitals. In veterinary medicine and the food sector there is continuous monitoring of the resistance situation in relation to livestock, meat and dairy products. This is the responsibility of the Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial Resistance (ZOBA). Since 2019, moreover, veterinarians have been reporting all their antibiotic prescriptions to a central database (IS ABV). Another important monitoring body is the National Reference Center for Emerging Antibiotic Resistance (NARA), which can identify and characterise even new, previously unknown cases of antibiotic resistance.

So far there has been no systematic collection of data on the use of antibiotics in outpatient care by general practitioners. Yet it is the area of human medicine where most antibiotics are used.

As part of an NRP 72 project, researchers at the University of Basel developed a practical solution for gathering data on the prescribing practice of family doctors. They looked at health insurers' billing data to see when and from which practice individual patients received an antibiotic. Analysing a sufficient quantity of patient data enabled them to draw conclusions about the prescribing practice of doctors. The researchers developed automated processes to gather all the necessary information from the various data formats and structures of the different insurers. They were thus able to collect data on antibiotic usage in primary care in a completely automated and anonymised way, without creating any extra work for general practitioners. This method could be developed into a nationwide monitoring system, provided that all health insurers supply the relevant information, and technical solutions are devised to collate it.

The full picture would need to include the environment and establish the links between human and veterinary medicine

Antibiotic resistance can emerge in both human and veterinary medicine – and is transmissible between people, animals and the environment. Yet the current monitoring system enables the transmission pathways between these areas to be traced only to a limited extent, and it does not cover the environment at all. One reason for this drawback is that little is so far known about the key interfaces at which resistance is transferred. For instance, we know little about how strongly and under what circumstances pathogen-resistance that has emerged in animals has an impact on human beings.

However, a better understanding and better monitoring of these interfaces could lead to more targeted measures that would reduce the spread of resistance between the different areas. This would also be important in terms of prioritising and testing the efficiency of new measures, such as when there are plans to introduce further changes in livestock farming that could have a big financial impact.

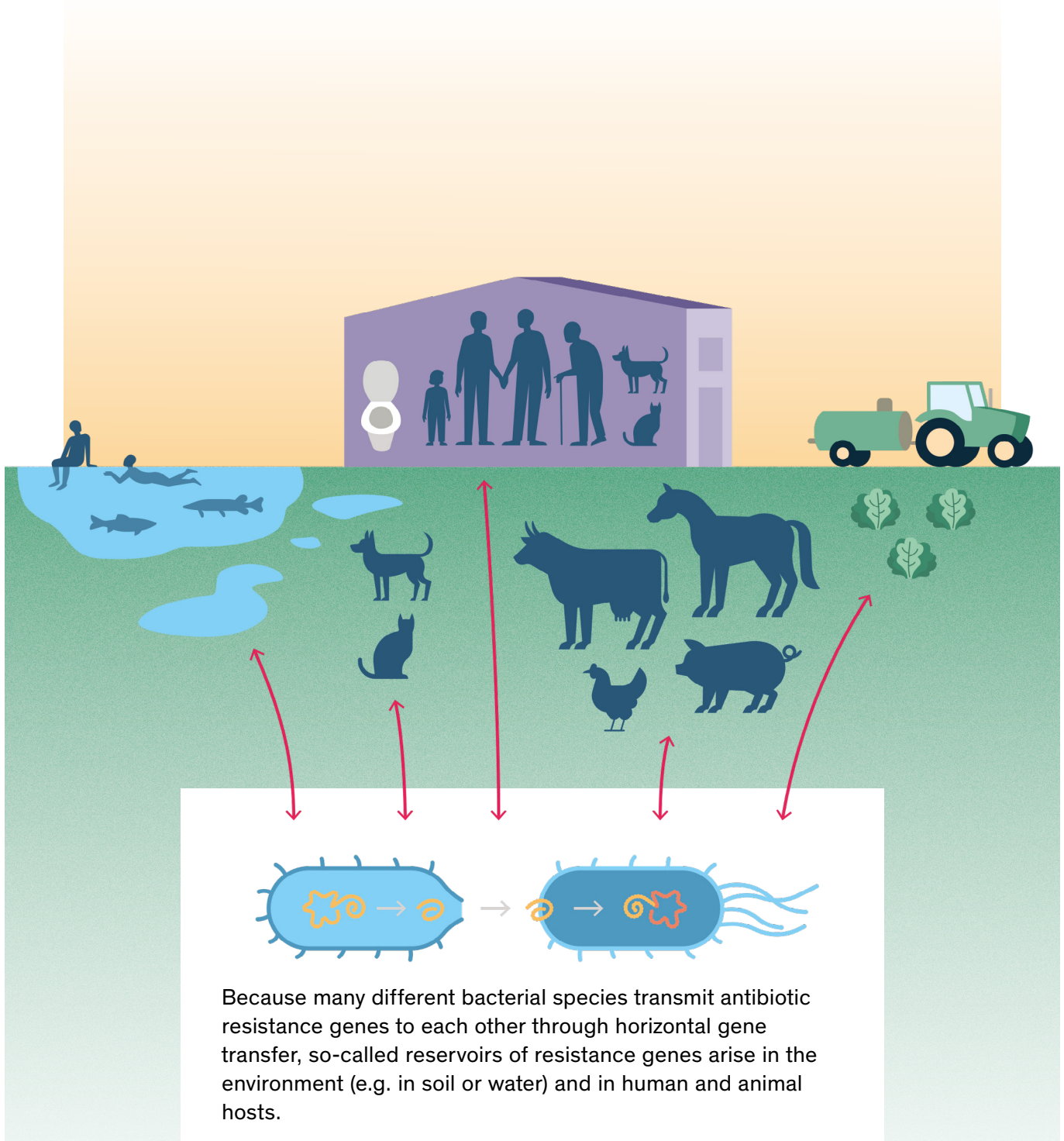
The problem: the transmission routes of antibiotic resistance are difficult to trace

Many antibiotic-resistant bacteria can colonise both people and animals. However, what makes the spread of antibiotic resistance particularly hard to track – unlike, for example, a virus such as SARS-CoV-2 – is the fact that it is due not only to the proliferation of the bacteria concerned, but also to mobile resistance genes being exchanged between bacteria. This means that once resistance or multi-resistance has emerged, it can be transmitted from one bacterium to another within a species, as well as between different species of bacteria.

Even non-pathogenic bacteria can therefore participate in the spread of medically problematic types of antibiotic resistance. Since bacteria colonise a variety of sites, reservoirs of antibiotic-resistance genes can form in the environment, including in soil and water, or in human or animal intestines. From there, resistance genes can in turn get onto pathogens, which incorporate them into their own genetic material and thus develop antibiotic resistance.

Complex dispersal through horizontal gene transfer

Antibiotic resistance spreads between human beings, animals and the environment. Many of these processes are hard to track, because different strains of bacteria can transmit antibiotic-resistance genes to each other. Even non-pathogenic bacteria thus participate in the spread of problematic types of resistance.



Whole genome sequencing: a new technology lays bare the connections

Systematic study of the way antibiotic resistance is transmitted throughout the entire human-animal-environment biological system has only been possible for a few years. It requires extensive genetic analyses of bacteria, covering mobile resistance genes as well as the entire genome. Resistance genes can thus be traced along different pathways, even where individual bacteria simply pass on the genes without being antibiotic-resistant themselves.

“Whole genome sequencing” (WGS) has become established as the key technology. It enables all, or nearly all, of an organism’s DNA sequences to be decoded in a short time.

NRP 72 research: new insights into key control points

NRP 72 researchers have used new gene sequencing technologies to investigate interfaces that are critical to the spread of antibiotic resistance. In many cases, their results provide the foundations for concrete measures to interrupt or restrict the transmission chains.

Human beings as resistance spreaders: international travel and home care

Project “Whole Genome and Plasmid Sequencing for MDR Enterobacteriaceae Simultaneously Isolated from Multiple Human and Non-Human Settings: Deciphering Impact, Risks, and Dynamics for Resistance Transmission and Spread”, Andrea Endimiani, University of Bern

Swiss tourists bring new types of antibiotic resistance back to Switzerland when they return from abroad. This has been demonstrated by researchers at the University of Bern who studied travellers to Zanzibar. On their return, a third of the tourists were shown to have multi-resistant bacteria in their intestines that had never been observed in Switzerland before. After being ingested in food in Zanzibar, antibiotic-resistance genes had spread to other bacteria in the intestinal flora by means of horizontal gene transfer.

Project “Understanding and modelling reservoirs, vehicles and transmission of ESBL-producing Enterobacteriaceae in the community and long term care facilities”, Stephan Jürgen Harbarth, University of Geneva

Patients who are found to have multi-resistant Enterobacteriaceae while in hospital may transmit them to other people after discharge. An international study in which Geneva University Hospitals participated has established that transmission to family members caring for patients at home frequently occurs, especially during the first two months after discharge from hospital.

Transmission from animals to people in the veterinary setting

Project “Whole Genome and Plasmid Sequencing for MDR Enterobacteriaceae Simultaneously Isolated from Multiple Human and Non-Human Settings: Deciphering Impact, Risks, and Dynamics for Resistance Transmission and Spread”, Andrea Endimiani, University of Bern

Antibiotic-resistant pathogens relevant to human medicine are widespread in small animal clinics, as an NRP 72 project at the University of Bern shows. In addition, the researchers demonstrated for the first time the transmission of multidrug-resistant *Escherichia coli* bacteria from hospitalised animals to employees at small animal clinics, while in the dog run of an animal clinic they discovered high-risk clones of *Klebsiella pneumoniae* which are resistant to almost all the available antibiotics. Genetic analysis revealed a high degree of kinship with pathogens found in animals in the same clinic.

Reservoirs outside the medical setting: wastewater, foodstuffs, manure

Reservoirs of antibiotic-resistance genes exist outside medical settings. This has been shown by a number of projects. Researchers at the University of Basel have demonstrated that extended-spectrum beta-lactamases (ESBLs: enzymes that make bacteria resistant to numerous antibiotics) are widely present in the wastewater of the City of Basel. The researchers also found pathogens with very similar extended-spectrum beta-lactamases in patients of Basel University Hospital, as well as in some foodstuffs available in the city's retail sector.

Project "Transmission of ESBL-producing Enterobacteriaceae and their mobile genetic elements – identification of sources by whole genome sequencing", Sarah Tschudin-Sutter, University of Basel

Researchers at the water research institute EAWAG measured elevated levels of antibiotic-resistance genes and antibiotic-resistant bacteria in rivers near to pipes from which treated wastewater from sewage plants is discharged. These levels are at any rate much lower than those seen in untreated wastewater, and they generally decrease quickly as the water moves downstream. In one river, the researchers nevertheless found significantly raised concentrations at individual sampling points located well below a sewage plant. They also observed that if sewage plant holding tanks overflow during heavy rain, high volumes of antibiotic-resistant bacteria and antibiotic-resistance genes are temporarily released in untreated wastewater directly into rivers.

Project "Swiss River Resistome – identity, fate, and exposure", Helmut Bürgmann, EAWAG

In vegetable farming, resistant bacteria can reach plants via manure. Researchers at Agroscope, the Swiss centre of excellence for agricultural research, have demonstrated this using the example of antibiotic-resistant *Escherichia coli* bacteria. While the bacteria themselves were detectable on salad leaves for only a few days, their most medically significant antibiotic-resistance genes were still present up to four weeks later.

Project "Tracking antibiotic resistance from environmental reservoirs to the food chain", Jörg Hummerjohann, Agroscope

An overall picture of the transmission routes of antibiotic resistance is possible

Thanks to new technologies, the research projects described were able to reveal in detail the interfaces involved in the spread of antibiotic resistance. They thus provide a basis for targeted measures. However, in order to obtain an overall picture of the transmission routes of antibiotic resistance and enable continuous monitoring of critical interfaces, these types of findings need to be brought together in a systematic way.

This requires the linking and joint analysis of genetic data from human medicine, veterinary medicine and the environment that has been generated using whole genome sequencing (WGS). In fact many laboratories active in the fields of human medicine, veterinary medicine and the environment are now routinely generating large amounts of WGS data anyway. Bringing it all together and analysing it does however require expensive technical infrastructure and highly developed database and bioinformatics competencies.

Also, the propagation patterns of antibiotic resistance can only be traced if the occurrence at genetic level is placed in context with epidemiologically significant information, such as the isolation date, location at which identified, type of infection, etc. This presents legal difficulties, because obtaining such information in relation to samples from human medicine involves patient data, too. However, this kind of data is particularly sensitive and is subject to special legal provisions.

NRP 72 research: the Swiss Pathogen Surveillance Platform brings everything together

Project "Development of a Swiss surveillance database for molecular epidemiology of multi-drug resistant pathogens", Adrian Egli, University of Basel

As part of an NRP 72 project, researchers at the Universities of Basel, Lausanne, Bern and Geneva, together with the Swiss Institute for Bioinformatics SIB, have developed a database which can jointly analyse both whole genome sequencing data and epidemiological data from a huge variety of areas. The Swiss Pathogen Surveillance Platform (SPSP – www.spsp.ch) was built step by step in close collaboration with health authorities and potential data providers and users. It now allows the collection and evaluation of genetic epidemiological information on multi-resistant bacteria, viruses and fungi from all the universities, university hospitals and veterinary medicine centres in Switzerland.

The SPSP proved its worth during the Covid-19 pandemic, during which it has been intensively used to exchange over 140,000 SARS-CoV-2 genomes while delivering automated, prompt reports to the FOPH on the analysis of different virus variants and their development. In order to monitor antibiotic resistance, the SPSP could additionally be connected with data on samples taken from food, agriculture and the environment in order to discover and monitor the propagation patterns of antibiotic resistance across the entire human-animal-environment biological system. Since the SPSP uses internationally established data standards, it can also link up with international monitoring networks, which increasingly contain WGS data.

Whole genome sequencing combines monitoring, diagnostics and the development of new antibiotics

Whole genome sequencing is becoming ever more firmly established in medical diagnostics. The technology is being used for the precise characterisation of pathogens in relation to infections, and to produce their antibiotic resistance profiles. This helps doctors choose the appropriate treatment. The data obtained could also be used for WGS-based monitoring of antibiotic resistance in real time. Similarly, up-to-date genetic data derived from monitoring a new resistance gene, for example, is enormously valuable for the correct interpretation of diagnostic tests.

Furthermore, the development of new antibiotics or vaccines can benefit from whole genome sequencing data obtained from monitoring and diagnostics. This is because such data shows exactly which genes and molecular properties make pathogens resistant to antibiotics. The information can be used to adapt active substances so that they combat resistance in a targeted way.

The Swiss Pathogen Surveillance Platform

The Swiss Pathogen Surveillance Platform (SPSP) enables Swiss universities, university hospitals and veterinary medical centres to analyse genetic and epidemiological data on antibiotic-resistant bacteria from many different sources. The SPSP thus provides the basis for monitoring the spread of resistance across humans, animals and the environment in far greater detail and more comprehensively than ever before.



Summary and recommendations

Thanks to recent technological advances in gene sequencing, it is now possible to investigate the spread of antibiotic resistance in much greater detail and much more comprehensively than ever before. Whole genome sequencing has emerged as the key technology for doing so. Several NRP 72 projects used whole genome sequencing to discover important interfaces and links in the processes by which antibiotic resistance spreads. By doing so they have delivered the basis for concrete measures to disrupt these processes.

Furthermore, the methods and technologies that are now being successfully used could potentially deliver the most comprehensive overview ever – one that encompasses humans, animals and the environment – of the routes by which antibiotic resistance spreads. To do so, however, they need to be strategically developed and used beyond the research environment with the aim of systematically monitoring antibiotic resistance. Furthermore, since whole genome sequencing in particular is being used ever more frequently in medical diagnostics, the monitoring and diagnosis of antibiotic resistance could benefit substantially from each other. The Swiss Pathogen Surveillance Platform (SPSP) set up in an NRP 72 project provides a basis for this development.

NRP 72 recommends

- taking action to break transmission chains at the antibiotic resistance transmission interfaces identified by NRP 72.

This includes, among other things, adapting infection control and prevention programmes in veterinary clinics, upgrading sewage treatment plants to include retention basins, informing and sensitising discharged hospital patients in whom antibiotic-resistant pathogens were detected while they were in hospital.

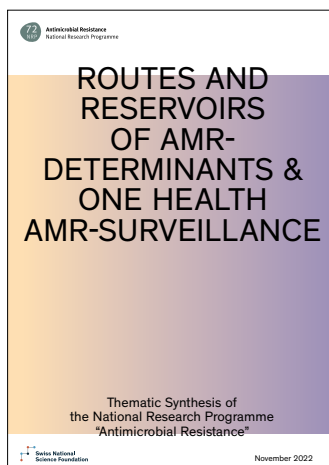
Implementing measures in human and veterinary healthcare institutions is primarily the responsibility of the institutions in question; in wastewater treatment it is the responsibility of the cantons.

- augmenting antibiotic resistance monitoring in all areas (humans, animals and the environment) with whole genome sequencing data, and jointly analysing these data.

The Swiss Pathogen Surveillance Platform should be expanded and suitably mandated as a key instrument that already fulfils the primary technical, legal and organisational requirements. In the environmental field, suitable control points should first be defined. Wastewater monitoring of the type introduced for SARS-CoV-2 would seem appropriate.

Implementing these measures is primarily the task of the Confederation.

The national StAR strategy provides a suitable framework within which the Confederation can initiate implementation of these measures, coordinate the relevant key players and mandate certain of them. Many measures could be rapidly implemented by individual players. By contrast, establishing comprehensive whole-genome-sequencing-based monitoring of antibiotic resistance demands long-term strategic planning involving a large number of stakeholders.



The thematic synthesis “Routes and reservoirs of AMR-determinants & One Health AMR-surveillance” summarises the research on the emergence and spread of resistance that has been carried out under NRP 72 and formulates detailed conclusions and recommendations in this area. The latter have been drafted in collaboration with researchers and numerous stakeholders.

See www.nrp72.ch

3

Curbing the emergence
of resistance:
prevention and optimised
use of antibiotics

Using antibiotics in a more targeted manner to restrict the emergence of resistance

Antibiotic use will always lead to antibiotic resistance. The crucial factors, however, are how quickly it happens, how many different types of resistance appear at the same time and how fast they propagate. If the pressure of these developments is not excessive, individual infections caused by resistant bacteria can be treated with alternative antibiotics. The incidence of existing antibiotic resistance may also decrease if the selection pressure caused by the respective antibiotic is reduced.

In an NRP 72 project at the University of Fribourg, researchers demonstrated that when several farms completely avoided using the antibiotic colistin, the large amounts of problematic colistin-resistant *Escherichia coli* microbes previously present were observed to decline to a very low level.

Project "Dynamics of transmission of polymyxin resistance genes in Enterobacteriaceae; from the environmental source to the patient", Laurent Poirel, University of Fribourg

For many years now there has been high and increasing use of antibiotics throughout the world, often in an untargeted way, which repeatedly leads to new types of antibiotic resistance. More and more often these combine and propagate rapidly thanks to global flows of goods and people. This trend can only be curbed if the use of antibiotics is rigorously optimised and, where possible, reduced in all spheres of application.

Prevention: preventing infections makes the use of antibiotics unnecessary

Preventive measures have the biggest effect on the use of antibiotics: where there are no infections, drugs are not needed. The aim of preventive measures against antibiotic resistance is therefore to stop the transmission of bacterial pathogens generally. Since resistant pathogens are particularly likely to occur in hospital settings, strict rules on infection control and prevention have been introduced in human and veterinary hospitals in Switzerland. These include clear instructions on hand hygiene and on isolating infected patients, for example.

Where humans are concerned, there is also an increased focus on transmission pathways outside the medical setting, with people taking individual steps to avoid infection. The latter include ensuring the safe preparation of certain foodstuffs such as poultry, or protecting oneself by avoiding shaking hands with infected people. Where animals are concerned, the focus is on livestock farming, where inadequate husbandry and hygiene encourage the transmission of infections. Here, prevention measures relating to operational procedures are particularly important.

Vaccines are another key element of prevention. They prevent an infection from becoming established. A number of diseases caused by bacterial pathogens have been completely or nearly eradicated in countries with sufficiently high vaccination coverage. These include tetanus (lockjaw), diphtheria and whooping cough. Some bacterial infections have been brought under better control through higher vaccination coverage with the vaccines now available. These include pneumococcal infections, which can cause meningitis and septicaemia, for example.

Preventing transmission to people outside medical settings: knowledge of the risks and appropriate communication are crucial

Outside medical settings, preventing the transmission of bacterial pathogens primarily depends on taking steps to protect oneself. It is therefore important that people are appropriately informed and made aware of the issues. Measures to avoid (viral and bacterial) infections have received considerable attention because of the Covid-19 pandemic, but there are other specific risks relating to antibiotic-resistant microbes. Several NRP 72 research projects have revealed some of these (see page 27/28). They include, for example, caring for patients discharged from hospital who are carrying resistant pathogens. These risks, too, can still be minimised with appropriate behavioural measures.

Project "Developing an evidence-based intervention for consumers to reduce the risk of multiple antimicrobial resistance transmission pathways", Vivianne Visschers, FHNW

People's willingness to adjust their own behaviour for protective purposes nevertheless depends on a number of psychological factors. In one NRP 72 project, researchers at Northwestern Switzerland University of Applied Sciences helped identify the decisive factors in consumer handling of raw meat that may contain resistant pathogens. On this basis they developed and tested various interventions for informing people and raising their awareness. It was found that interventions adjusted to individual psychological factors are better at motivating people to change their behaviour than simply giving them information.

Prevention in livestock farming: adapting operating processes has great potential

In recent years the use of antibiotics in livestock farming has fallen significantly in Switzerland. The biggest advances are attributable to preventive measures that inhibit the spread of infectious diseases and improve animal health in general. Major poultry producers, for example, have switched to the all-in-all-out system, where all the birds enter the previously cleaned and disinfected pens at the same time and stay there until slaughter, without any other birds being brought in from outside during the entire cycle.

Project "Resistome in the pig farms: Comparison of the breeding and fattening units with a One Health approach", Markus Hilty, University of Bern

An NRP 72 project at the University of Bern has shown that pig farms using the all-in-all-out system have the lowest levels of antibiotic-resistant microbes.

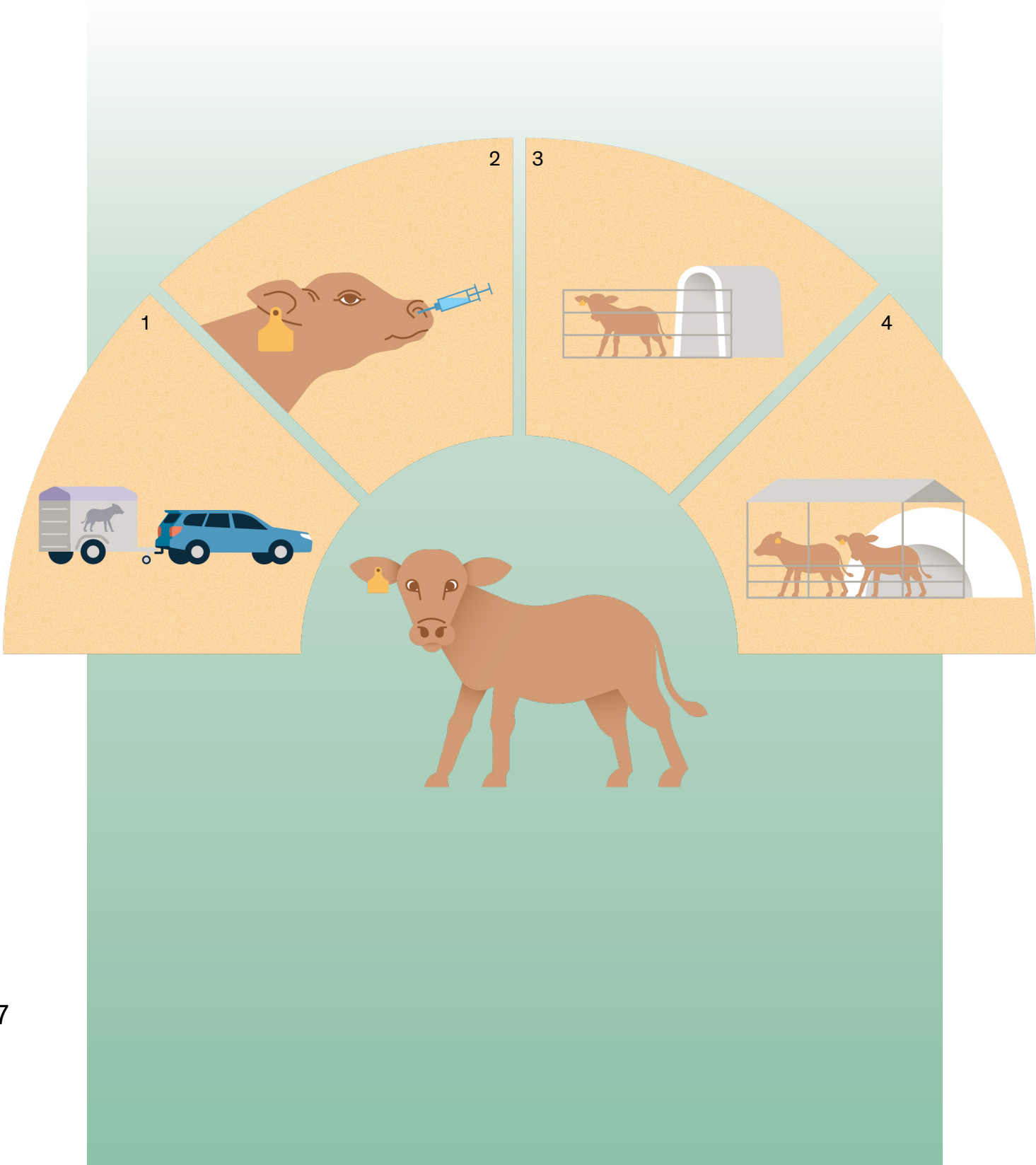
Project "A novel concept for veal calf production: 'the outdoor veal calf'", Mireille Meylan, University of Bern

Veal calf production is one of the sectors of animal husbandry with the highest consumption of antibiotics. However, it could be carried out successfully with much lower antibiotic consumption. NRP 72 researchers at the University of Bern have therefore developed a new fattening concept called the "outdoor veal calf". In a case study, this led to an 80% reduction in the use of antibiotics. The "outdoor veal calf" concept combines a number of measures with the principal aim of avoiding infections with pneumonia pathogens (see page 37). This is because pneumonia is the most common

reason for administering antibiotics in veal calf production. In addition to the drastic reduction in the use of antibiotics, the researchers found a lower incidence of antibiotic resistance on the test farms at the end of the fattening period. All this was achieved by improving the health and welfare of the animals. At the same time, switching to the “outdoor veal calf” concept had no impact on economic efficiency.

Outdoor calves: fewer antibiotics in veal calves

The “outdoor veal calf” concept of veal calf production reduces antibiotic use thanks to measures for preventing infection: 1) Newly purchased calves are not mixed with calves from other producers during transport. 2) The calves are vaccinated against pneumonia on arrival at the feedlot. 3) For their first two weeks on the farm, the calves are kept under quarantine in individual igloo-type hutches. 4) The calves spend the rest of the fattening period in small groups in outdoor hutches with sheltered, straw-bedded outdoor pens.



Using antibiotics in a more targeted way when infections occur: improvements possible in human and veterinary medicine

Giving up antibiotics completely is not a solution. Instead, they should be used in a much more targeted manner: that is, in the presence of a bacterial infection requiring treatment. This applies to both human and animal patients. On the other hand, unnecessary or improperly used antibiotics not only speed up the development of antibiotic resistance but often lead to worse treatment outcomes, since they do not have the desired effect.

A variety of factors can lead to antibiotics not being optimally prescribed. These include the fact that doctors often have to decide on treatment before it is clear which pathogen is responsible for an infection, whether it is resistant, and to which drugs. They often do not have access to up-to-date treatment guidelines that reflect the current drug-resistance situation. Studies performed in both inpatient and outpatient settings repeatedly judge a proportion of antibiotic prescriptions for human patients to be inappropriate. The same applies in veterinary settings.

Antimicrobial stewardship programmes assist prescribing practice

“Antimicrobial stewardship” programmes have been set up to optimise the use of antibiotics. These are packages of measures implemented either at an individual medical institution or at regional or national level. Their key components include continuous measurement of prescribing practice and the drug-resistance situation, giving feedback to professionals issuing prescriptions, and providing tools to help them select the appropriate antibiotic (or none at all) in the correct application for individual cases.

In human medicine in Switzerland, it is mainly the larger hospitals that have their own stewardship programmes. Since 2017, the National Centre for Infection Prevention (Swissnoso) has been evaluating this kind of programme and drafting best-practice guidelines for individual healthcare institutions as well as for the nationwide coordination of these efforts. At present there are no major stewardship programmes for outpatient medicine. In veterinary medicine, an online tool called AntibioticScout that was developed in an NRP 72 project is now in use. This web portal helps veterinarians prescribe on the basis of general treatment guidelines and the current drug-resistance situation.

NRP 72: interventions to optimise the prescription of antibiotics in human and veterinary medicine

In a number of NRP 72 projects researchers have developed and tested interventions to reduce or optimise the use of antibiotics in human and veterinary medicine.

Online tool for veterinarians

NRP 72 researchers at the University of Zurich developed an online tool called AntibioticScout for veterinarians. This contains up-to-date recommendations regarding selection, dosage, application and treatment length for antibiotics. AntibioticScout has been accessible by all veterinarians since 2016. In one study, the researchers were able to demonstrate that during a two-year observation period following the launch of AntibioticScout, antibiotic use fell for all species of animal. Although AntibioticScout was initially limited to treatments for livestock, the researchers later widened its scope

Project “AntibioticScout: Online tool for antimicrobial stewardship in veterinary medicine”, Hanspeter Naegeli, University of Zurich

to include domestic pets, exotic species and horses. The online tool has now become established and is also used in veterinary training and professional development.

Feedback on antibiotic prescribing in hospitals

Project "Implementation of routine audit and feedback on the use of protected anti-Gram-negative antibiotics: a multicenter, randomized trial using segmented regression analysis of interrupted time series", Laurence Senn, University of Lausanne

To support doctors with prescribing antibiotics in hospitals, researchers at the University of Lausanne developed and tested a programme in which infectious disease specialists provided training, reviewed doctors' prescribing practices weekly and gave them a direct feedback. In addition, a website provided information for the prescribing doctors. This six-month intervention led to a slight fall in the use of critical antibiotics. The smallness of the reduction as measured in numbers was partly explained by the fact that prescribing practice was good overall, with around three-quarters of the prescriptions in the study being assessed as correct.

Digital support for hospital doctors

Project "COMPASS study (COMPUTerized Antibiotic Stewardship Study)", Benedikt Huttner, University of Geneva

In a project at the University of Geneva, researchers tested a method which assisted hospital doctors with prescribing antibiotics during actual consultations by displaying treatment guidelines directly in the respective hospital's patient files. If a doctor deviated from these, they had to state the reason in the patient files. In a study conducted in three hospitals, this intervention did not lead to a reduction in antibiotic prescriptions, but it did improve the quality to some extent. The researchers think that the possible reasons for the lack of reduction are the already relatively low use of antibiotics together with a lack of user-friendliness, which they hope to improve. In a further study, they are testing a smartphone app to improve antibiotic usage. Initial findings (as of November 2022) have shown that demand for this user-friendly tool is very high, particularly among younger doctors.

Feedback on antibiotic prescriptions in primary care

Project "Routine antibiotic prescription and resistance monitoring in primary care physicians: A nationwide pragmatic randomized controlled trial", Heiner C. Bucher, University of Basel

In an NRP 72 project, researchers at the University of Basel conducted a randomized controlled trial with the goal to reduce antibiotic prescription in high-to-medium antibiotic prescribing general practitioners. For this, they arranged for feedback to be sent every three months to over 1500 family doctors. This occurred anonymously, and the researchers did not know the doctors' names. In addition they informed them – also anonymously – at the start of the study about the current drug-resistance situation and average antibiotic use at other doctors' practices in their region. 1500 practitioners randomised to the control group were not informed about the trial but their antibiotic prescription was registered. The intervention did not, however, lead to any improvement in prescribing practice during the two-year study. Nevertheless, this project enabled the researchers developed the basis for monitoring antibiotic prescriptions in primary care (see page 25). This is a vital condition for targeted stewardship programmes.

Better diagnosis thanks to rapid tests

Family doctors prescribed antibiotics for respiratory infections around a third less often thanks to a different intervention: researchers at the University of Lausanne developed a diagnostic procedure that combines ultrasound examination of the lungs with a rapid procalcitonin test which helps differentiate between bacterial and viral infections. Since the two methods alone produce too many unreliable diagnoses, the researchers combined their results with an algorithm to increase diagnostic precision. In a practical study, this combination achieved a marked fall in prescriptions with no loss of treatment quality. However, a surprising finding was that the procalcitonin test alone was sufficient to bring about the reduction. Based on these results, the Swiss Society for Infectious Diseases has added the use of the procalcitonin test to its guidelines on the therapeutic management of pneumonia. The researchers have also shown in a further study that the method is cost-effective. This is important, because its widespread use depends on the health insurers paying for it.

Project "Procalcitonin and lung ultrasonography point-of-care testing to decide on antibiotic prescription in patients with lower respiratory tract infection at primary care level: pragmatic cluster randomized trial", Noémie Boillat Blanco, University of Lausanne

Diagnostics – the basis for therapy decisions

Diagnostics may provide the best basis for the targeted use of antibiotics. When both the type of pathogen and its resistance profile are known, doctors are able to select the appropriate antibiotic therapy. They can also use appropriate diagnostics to monitor its success, so that an antibiotic is not delivered for longer than necessary, or they can switch to a different one at the right time.

Most of the tests in use today, however, take around 36–48 hours to identify and characterise a pathogen reliably. In many cases doctors cannot wait that long. They need to commence treatment before they have exact information about the pathogen, so they often forgo a precise diagnosis. This leads to inappropriate antibiotic prescriptions, because the drug-resistance profile of a bacterial pathogen cannot be taken into account or because there is often no bacterial pathogen involved at all. The lack of rapid tests also means that doctors are more likely to have recourse to broad-spectrum antibiotics in order to increase the chances of therapeutic success. Again, this favours the development of antibiotic resistance.

New tests: speed and detailed information

Against this background, the development of diagnostic tests has grown in significance. Two aspects are important: tests need to be rapid, while also giving as much information as possible about the resistance present. This means not simply finding out which antibiotic or antibiotics a pathogen is resistant to, but also which gene is responsible for the resistance, for example. As described in Chapter 2, whole genome sequencing technology is therefore becoming increasingly important. At the same time, a number of established and new approaches facilitate rapid tests on particular pathogens and resistances. There is great demand for such tests in day-to-day clinical practice.

NRP 72: tried-and-tested methods and new technologies for faster diagnosis

Several NRP 72 projects investigated new diagnostic tests which deliver results more rapidly than the current tests. This involved tried-and-tested methods of clinical diagnosis alongside technologies that are largely unknown in this area.

Developing established diagnostic methods further

Project "Rapid diagnostic tests for detection of antibiotic resistance in clinically-significant Gram-negative bacteria", Patrice Nordmann, University of Fribourg

In an NRP 72 project at the University of Fribourg, researchers were able to enhance established microbiological diagnostic methods so that they produced results after a period of just 30 minutes to three hours. One reason for this success is that they always selected – and wherever possible optimised – the most promising method for detecting different pathogens. This was the case with culture-based methods, for example, in which bacteria are first isolated from samples and then placed in a culture medium in which they multiply. It has recently become possible to greatly accelerate the reproduction of different species of bacteria by using specially adapted culture mediums, and the researchers were able to exploit this in new tests. Some of the tests have already been implemented in practice.

Diagnosis using optical fibres

Project "A new rapid and reliable bacterial phenotypic diagnostic technique detecting bacterial susceptibility to antibiotics using optical fibers", Sandor Kasas, EPF Lausanne

Researchers at EPF Lausanne have developed a completely new type of test to measure the susceptibility of pathogens to antibiotics. It is considerably faster than previous tests. In their procedure, individual living bacteria are isolated from patient samples and attached to hair-thin carriers. The movements of the bacteria are transmitted to the carriers, whose vibrations are plotted by a laser and visualised on a computer screen. When a bacterium responds to an antibiotic, it dies and the carrier's movement comes to an immediate halt. Conversely, if the carrier continues moving, the bacterium is resistant to the antibiotic administered. The researchers founded a start-up company which has made use of the method in an easy-to-use diagnostic device.

Diagnosis using microchips

Project "Microfluidic device for ultrarapid phenotypic susceptibility testing of pathogenic microbes", Petra Dittrich, ETH Zurich

A diagnostic method newly developed by researchers at ETH Zurich involves capturing small quantities of microbes on a microchip. The microchip has hundreds of tiny compartments filled with nanoparticle oxygen sensors and antibiotics. Bacteria susceptible to the antibiotic in question subsequently die, while any that are resistant survive. Survival can be determined microscopically from the oxygen consumption of the bacteria. In trials using different species of bacteria, the researchers were thus able to distinguish clearly between sensitive and resistant bacteria. The microchip-based method is fundamentally suited to the rapid diagnosis of antibiotic resistance and is especially helpful in the case of slow-growing bacteria.

Diagnosis using nanosensors

Using another technology completely new to the field of diagnostics, researchers at the University of Basel were able to obtain extremely accurate test results very rapidly. Their procedure uses microscopically small sensors (nanomechanical cantilevers) coated with different biomarkers. These markers precisely match the shape to which individual and very specific genetic sequences of a bacterium bind. As a result, they can be designed to specifically bind those sequences that are responsible for various types of resistance. When a bacterial sample containing the relevant sequence comes into contact with a nanosensor, the surface tension of the sensor is measurably changed. This change shows whether a pathogen possesses a specific resistance. Having successfully completed their initial trials, the researchers now want to focus on diagnosis in the presence of sepsis, since the rapid detection of antibiotic resistance is particularly important in this situation and potentially means the difference between life and death.

Project "Fast Assessment of antibiotic resistance in bacteria by using nanomechanical arrays", Ernst Meyer, University of Basel

Detection of pathogens by small antibodies

One approach for faster diagnostic processes is the use of antibodies to show the presence of specific bacterial pathogens directly in a blood sample. However, traditional antibodies are not suitable for this, as they generally recognise highly variable sugar chains, which differ between various strains of the same bacterial species. A team at the University of Zurich has therefore targeted conserved protein structures, which barely differ within the same bacterial species. Their binding sites are hardly accessible for whole antibodies, but can be readily located with much smaller antibody fragments known as nanobodies. The researchers developed different nanobodies to detect and capture the clinically important pathogen *Escherichia coli*. They have already succeeded in this in laboratory tests. In a next step, they are now generating further nanobodies to be able to detect a broader spectrum of pathogens. At the same time, they are simplifying the necessary procedures and processes so that this approach can be used in routine diagnostics.

Project "Rapid diagnostics of blood stream infections using synthetic nanobodies", Markus Seeger, University of Zurich

Antibiotic stewardship in human medicine

“Antibiotic stewardship” programmes support physicians in the rational and responsible use of antibiotics. These programmes include training and specific interventions such as regular feedback, as well as appropriate diagnostic tools. The programmes also create a framework that gives high priority to the responsible use of antibiotics. NRP 72 projects have developed and tested solutions that contribute to effective antibiotic stewardship programmes.

Leadership and responsibility

- Health and hospital administrations devote sufficient human and financial resources to antibiotic stewardship
- Antibiotic stewardship programme leaders take responsibility for the implementation and outcome of the programmes

Expertise
Infectious disease specialists ensure that antibiotic stewardship is implemented in a professionally rigorous manner

Targeted interventions
Clearly defined interventions should measurably improve antibiotic prescribing

Monitoring
An exact picture of antibiotic prescribing in an institution makes it possible to target interventions and to measure success

Reporting and communication
Physicians regularly receive straightforward feedback on their prescriptions, current treatment guidelines and the resistance situation

Training
Continuous training in treatment and diagnosis reinforces good prescribing practice among physicians

Diagnostics
Appropriate diagnostic methods and simple, fast processes at the points of interface with laboratory diagnostics support treatment decisions

Summary and recommendations

In view of the long-term links in the emergence and spread of antibiotic resistance across humans, animals and the environment, antibiotic use should be reduced or optimised wherever possible. This applies as much to human medicine as to veterinary medicine. Prevention plays a significant role here, but it is important that professionals lend their support through their prescribing habits too.

In Switzerland, the nationwide Strategy on Antibiotic Resistance (StAR) has been the driver of both fields of activity in human and veterinary medicine. However, research from NRP 72 shows that there is still plenty of scope for further optimising and reducing antibiotic use, and this is an area where it is delivering newly developed and tested interventions.

NRP 72 recommends

- systematically pursuing the current federal-level efforts to improve animal welfare and health, and, within these efforts, focusing on preventing infection in animal facilities.

The Confederation should actively support the “outdoor veal calf” concept in this context, including recognising it for direct payments.

Implementing these measures is primarily the task of the Confederation and animal producers.

- constantly refining veterinary treatment guidelines and incorporating them in the AntibioticScout online tool.

This measure is already being implemented in cooperation between the Confederation and veterinary organisations.

- implementing long-term antibiotic stewardship programmes in hospitals according to criteria defined by the National Center for Infection Control (Swissnoso) and taking account of new insights from NRP 72.

First and foremost, implementing antibiotic stewardship programmes at hospital level requires commitment from the governing bodies of the institutions in question and from the health departments of the individual cantons. Research findings and synthesis work from NRP 72 highlight the need to create stronger obligations in this area than has previously been the case.

- developing a national strategy to promote good antibiotic prescribing habits in human primary care.

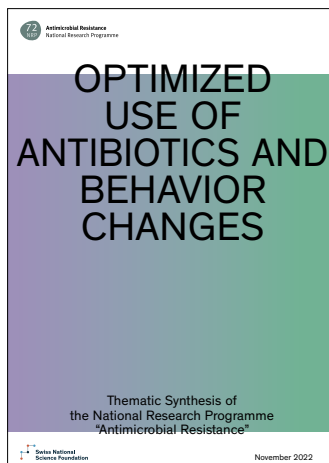
This strategy must be based on continuous antibiotic prescription monitoring of the type that already exists in veterinary medicine. To this end, implementation of the health-insurance-data-based method developed in NRP 72 should be examined.

Planning and implementation of this measure is primarily the task of the Confederation and the cantons.

- accelerating approval procedures for new diagnostics and adequately reimbursing their use in practice.

Reimbursement schemes should incentivize medical doctors, diagnostic laboratories, and hospitals to adequately use and constantly improve diagnostic testing.

The national StAR strategy provides a suitable framework within which the Confederation can initiate implementation of these measures, coordinate the relevant key players and mandate certain of them. However, other federal-level developments – specifically the continued development of agricultural policy currently being discussed by parliament – are also important, particularly for animal production. By contrast, the cantons are key to implementation in human medicine.



The thematic synthesis “Optimized use of antibiotics and behavior changes” summarises the NRP 72 research that developed and tested interventions aimed at reducing and optimising antibiotic usage. It formulates detailed conclusions and recommendations in this area, which have been drafted in collaboration with researchers and numerous stakeholders.

The NRP 72 research on new diagnostic methods is presented in the thematic synthesis “Faster diagnostics and new therapeutic approaches”.

See www.nrp72.ch

4

Overcoming
existing types of resistance:
new antibiotics

There is a constant need for new therapies

Globally, more and more multi-resistant pathogens are emerging which can no longer be treated using the antibiotics available. This kind of resistance will continue to spread, and new types will appear. The need for new active substances is therefore rising. Of particular importance in this respect are medicines based on new modes of action, which circumvent existing types of resistance and thus can be used to treat multi-resistant bacteria. For some time now, however, hardly any new classes of antibiotics have come onto the market (see page 21).

The development of new antibiotics is currently lagging far behind the increase in drug resistance. But even if the latter can be attenuated, new antibiotics and other treatment options will constantly be needed.

NRP 72: big potential for new antibiotics and alternative therapeutic approaches

Several NRP 72 projects researched new antibiotic therapies, using a wide variety of methods. The results of these projects show that antibiotic resistance can be overcome with novel modes of action.

Developing existing antibiotics further

It is now becoming increasingly possible to establish the relationship between the molecular structure of an active substance and its mode of action. This also applies to the aminoglycosides, a class of antibiotics effective against major hospital pathogens and therefore of great importance. Yet, increasingly, we are seeing resistance emerge even against them. Such resistance could be overcome by modifying the structure of aminoglycosides themselves in a targeted way. However, that requires a detailed understanding of the relationships between structure and action. In a project at the University of Zurich, researchers have clarified these relationships to the point that they have been able to create aminoglycosides which, with minimal modifications, exhibit promising activity against antibiotic-resistant *Pseudomonas aeruginosa* bacteria. This work provides a basis for the targeted further development of aminoglycosides.

Project "Aminoglycoside Drug Development", Erik Christian Böttger, University of Zurich

Systematic search for new antibiotics in nature

Project "Ecosystem- and genome-guided antibiotic discovery", Jörn Piel, ETH Zurich

Researchers at ETH Zurich have developed a bioinformatics platform that can be used to search systematically for previously unknown antibiotic substances in nature. The new methods look at the genetic information of microorganisms in order to work out whether they can produce such substances, even if they do not do so in their natural environment. Using this approach, the researchers found a whole range of new anti-biotically active substances with previously unknown chemical structures on the surface of leaves, in the roots of plants and in sea sponges. Some of these substances are now being followed up by other research groups, which are testing their medicinal potential and developing them further. Thanks to the methods developed in this project, many other novel and promising antibiotic substances from a wide range of ecosystems are likely to be discovered in the next few years.

Determining the structure of newly discovered active substances

Project "The molecular mechanism of outer membrane protein insertion by BamA and its role as a target for novel antibiotics", Sebastian Hiller, University of Basel

Another active substance that was discovered in the natural world a few years ago is darobactin, which is produced by nematodes for defence against bacteria. Darobactin raises high hopes of a new class of antibiotics: in laboratory tests, it is effective against nearly all the most difficult-to-treat antibiotic-resistant pathogens. Researchers at the University of Basel attracted considerable attention in scientific circles worldwide for their success in explaining darobactin's particular mode of action. Thanks to the realisation that the special three-dimensional structure of darobactin makes all the difference, it is now possible to improve the substance in a targeted manner and develop it into an effective medicine. These preclinical development steps are currently underway in collaboration with a medium-sized biotech company.

Designing new chemical structures

Project "Antimicrobial peptide dendrimers (AMPD) and bicyclic peptides (AMBP) as therapeutic agents against multidrug resistant bacteria", Jean-Louis Reymond, University of Bern

Researchers at the University of Bern looked for an alternative to the antibiotic colistin, which is currently used as a drug of last resort against many multi-resistant germs. Yet it can have considerable side effects, and some bacteria have now become resistant to it. The researchers looked for chemical structures as similar as possible to that of colistin, but they did not do so in nature: instead, they searched what is known as "chemical space", which represents all theoretically conceivable molecules. In this way, the researchers were able to identify and artificially manufacture several substances which turned out to be effective against many problematic microbes in laboratory tests. One of these substances has proved suitable for the next steps towards the development of a drug.

Phages: viruses against antibiotic resistance

Bacteria have natural enemies: bacteriophages – i.e. viruses that affect bacteria – use bacteria as a host organism in which to replicate. When exiting from a bacterium they disrupt the bacterial cell wall by means of specific enzymes called endolysins, causing the bacterium to die. Researchers conducting a project at ETH Zurich were able to identify various endolysins that kill antibiotic-resistant *Staphylococcus aureus* bacteria, which often cause diseases in human beings. In order to introduce these endolysins to infection sites inside the body, the researchers added them to specific protein compounds which accumulate at very particular sites in the human body but do not occur elsewhere. Experiments showed that infections of the bone tissue could be treated in a targeted way using this method. Although the possibility of developing usable therapies is now in view, it will be difficult to achieve because this is an entirely novel approach, so the licensing criteria, to take one example, have not yet been clearly defined.

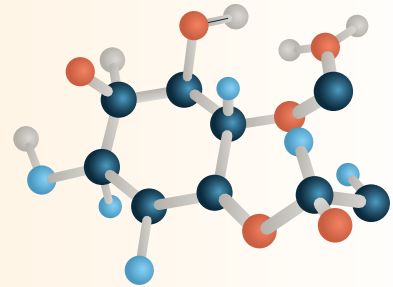
Project "Novel targeted bacteriophage endolysin-based approach for treatment of drug-resistant *Staphylococcus aureus* infections", Martin Loessner, ETH Zurich

Systematically searching for and generating new antibiotics

NRP 72 researchers have found and generated a number of new antibiotic agents to combat existing antibiotic resistance. The methods used in the projects are proving to be tried-and-tested tools that will enable academic research to produce additional active agents in the future.

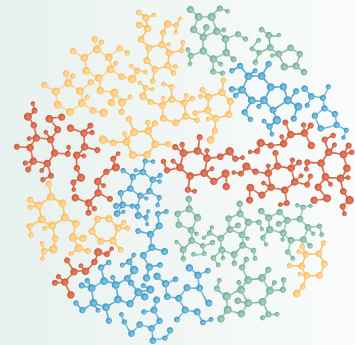
Improving existing and newly discovered active substances

Reveal links between the molecular structure and mode of action of substances to specifically improve active ingredients in terms of efficacy and side effects



New (artificial) molecules in chemical space

Starting from the chemical structure of proven antibiotics, explore all theoretically possible similar compounds, and synthesise and test promising agents



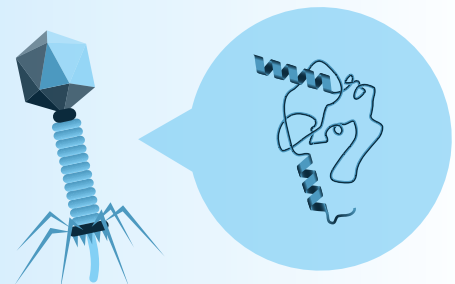
“Genome mining” in nature

Sequence the genome of microorganisms from many different habitats and use the gene sequences to assess whether they can produce previously unknown antibiotic agents



Bacteriophages

Modify enzymes that bacterial viruses (bacteriophages) employ to kill their bacterial hosts and target them to infection sites to act against specific pathogens



Successful research, but little chance of putting it into practice

The research carried out under NRP 72 has generated some very promising approaches for new antibiotics. One project took place in collaboration with a medium-sized biotech company, which is currently using the findings in preclinical research. However, that is very much the exception and there is no guarantee it will be developed further. After the initial development phases it is extremely rare for novel antibiotics to reach the next stage, which is usually the province of larger companies. The development costs are too high compared with the expected profits. Today, the main problem facing antibiotic development is primarily economic rather than scientific.

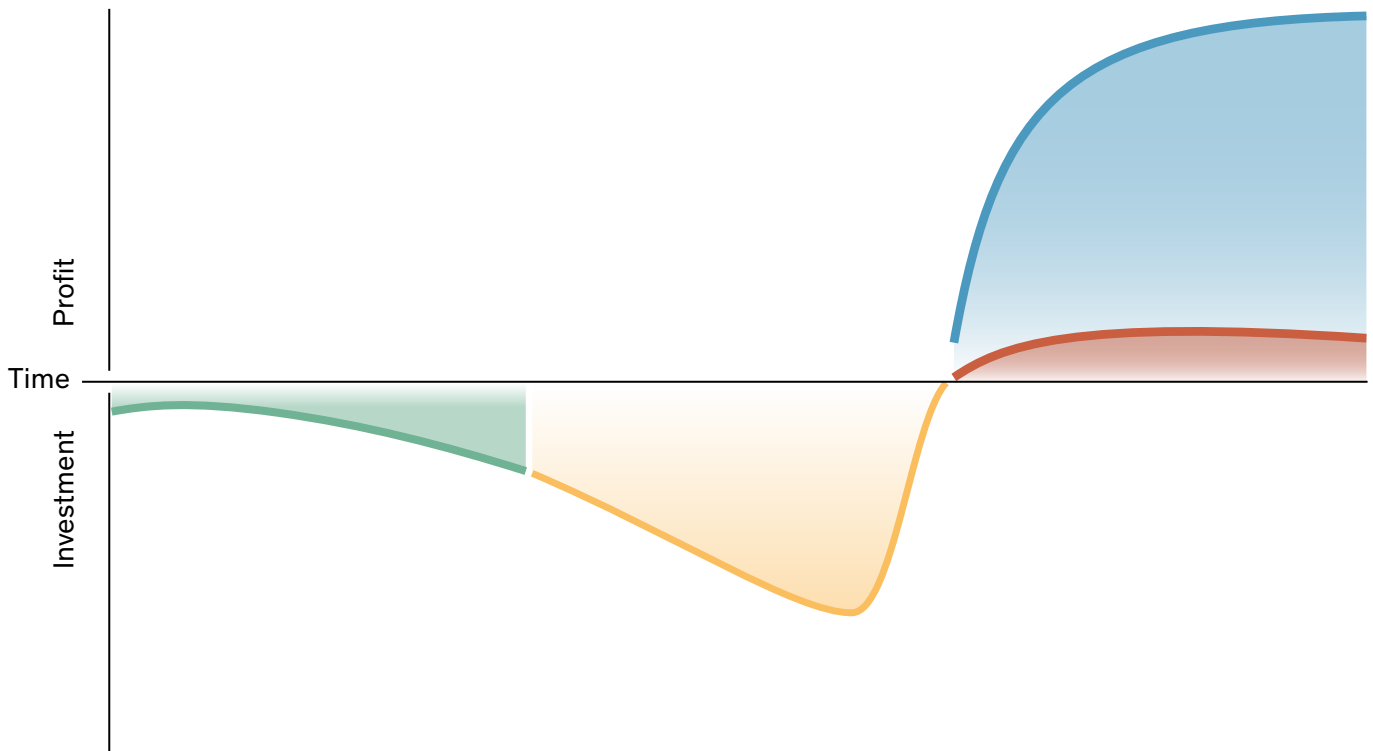
Market incentives needed as well as support for innovative research

Over the past few years governments and other funding agencies throughout the world have invested significant amounts in academic research in order to promote research on new antibiotics. The NRP 72 projects were also funded in this way. And with the National Centre of Competence in Research (NCCR) AntiResist, Switzerland will continue to have a strong academic research base for new therapeutic approaches in the coming years. Internationally too, driven by initiatives such as CARB-X and the Novo Repair Impact Fund, considerable funding has recently been made available for promising individual projects at small and medium-sized biotech and pharmaceuticals companies, whereby Swiss companies are regular recipients of contributions due to their innovative research.

All these activities focus on early-phase drug development. While they are important, they have not resulted in many new medicines to date. So far it has not been possible to bridge the gap between the early phases and clinical development, since the fundamental problem of the lack of market incentives has not been solved. This is why “pull-incentives” are currently discussed and implemented by some countries, like Sweden and the United Kingdom: mechanisms that provide incentives on the market side, such as in the form of substantial premiums to be received by the developing company when a novel antibiotic gains market authorisation. One of the basic principles of this model is that the potential profits are decoupled from the quantity of antibiotics sold.

Failing market incentives for antibiotics

Academic research contributes to the initial stages of drug development. Yet even promising approaches are rarely pursued thereafter. The risk of failure is high, and the steps required – from preclinical laboratory studies to trials with patients prior to approval – are increasingly costly. This is true for all drugs. However, since the profit expectation for antibiotics is very low – partly because novel antibiotics should be used as restrictively as possible – the usual market incentives do not work and hardly any new antibiotics are developed into mature drugs.



Basic research, e.g. academic research such as in NRP 72
Preclinical development (especially small and medium-sized companies)

Clinical development, mainly small and medium-sized companies in the early phases
and large pharmaceutical companies in the late phases

Expected profit after market approval:
well-functioning market, e.g. for antihypertensive drugs, cancer therapies, etc.

Expected profit after market approval:
market for antibiotics, as novel drugs should not be sold as reserve antibiotics
if possible and prices are regulated at low levels

Summary and recommendations

There is a huge need for new antibiotics and this is set to grow even further. Research by NRP 72 provides overall grounds for optimism. It shows that it is possible to overcome antibiotic resistance with novel antibiotic active substances. However, market conditions are unfavourable for their further clinical development into new drugs.

Indeed financial considerations are the primary reason why, for many years, far too few new antibiotics have been developed to market readiness. There is unanimity that market mechanisms have failed in this area. Various ways of overcoming this situation are currently being discussed. One feature common to them all is the need for governments to create new framework conditions in the antibiotics market that make it worthwhile developing antibiotic medicines to market readiness.

This is an area where Switzerland is in a unique position. It has strong basic research, a large number of start-ups and small and medium-sized companies, and a world-leading pharmaceutical industry. Thus it has the potential to make a significant and urgently needed contribution to the development of effective antibiotics, both globally and for itself. However, this will mean systematically combining the promotion of early-stage research with suitable market incentives. This will create a sustainable development environment in which a portfolio of new treatment approaches can be continuously driven forward.

If Switzerland takes a leading role in this area, it could gain major opportunities not only in new antibiotic supply, but also financially, since such engagement would strengthen the country as a centre of innovation.

NRP 72 recommends

- providing new economic incentives that make it worthwhile for industry to maintain long-term, diversified antibiotics programmes;

The legal and financial steps that must be taken in this area require government commitment at the national level. The government must give a clear mandate and define corresponding responsibilities.

- taking an active role in international initiatives that ensure the development of and access to new antibiotics;

The Swiss government must allocate the necessary funds and define responsibilities within the federal agencies.

- securing funding for excellent basic research and clinical development of antimicrobials in Switzerland.

Research funding organisations should create structures that ensure a strong focus on novel antibiotics in Switzerland's basic research in the long term. In addition, programmes supporting pre-clinical and clinical development of antibiotics should be implemented.



The thematic synthesis “Faster diagnostics and new therapeutic approaches” summarises the research on new therapeutic approaches carried out under NRP 72 and formulates detailed conclusions and recommendations in this area. The latter have been drafted in collaboration with researchers and numerous stakeholders.

See www.nrp72.ch

Overview of research projects

NRP 72

Contribution of natural transformation to the transmission of resistance genes in hospital-acquired pathogens **Project leader: Melanie Blokesch | EPF Lausanne**

Procalcitonin and lung ultrasonography point-of-care testing to decide on antibiotic prescription in patients with lower respiratory tract infection at primary care level: pragmatic cluster randomized trial
Project leader: Noémie Boillat Blanco | University of Lausanne

Towards quantification of the contribution of plasmids to the spread of antibiotic resistance **Project leader: Sebastian Bonhoeffer | ETH Zurich**

Aminoglycoside Drug Development
Project leader: Erik Christian Böttger | University of Zurich

Development of novel ribosome-targeting antibiotics
Project leader: Erik Christian Böttger | University of Zurich

Routine antibiotic prescription and resistance monitoring in primary care physicians: A nationwide pragmatic randomized controlled trial
Project leader: Heiner C. Bucher | University of Basel

ESBL-MS: Early diagnosis of ESBL Enterobacteriaceae in patient samples
Project leader: Dirk Bumann | University of Basel

Swiss River Resistome – identity, fate, and exposure
Project leader: Helmut Bürgmann | EAWAG

Microfluidic device for ultrarapid phenotypic susceptibility testing of pathogenic microbes **Project leader: Petra Dittrich | ETH Zurich**

Development of a Swiss surveillance database for molecular epidemiology of multi-drug resistant pathogens **Project leader: Adrian Egli | University of Basel**

Whole Genome and Plasmid Sequencing for MDR Enterobacteriaceae Simultaneously Isolated from Multiple Human and Non-Human Settings: Deciphering Impact, Risks, and Dynamics for Resistance Transmission and Spread
Project leader: Andrea Endimiani | University of Bern

Insights into the role of phages on the bacterial resistome
Project leader: Elena Gomez-Sanz | ETH Zurich

An interventional study to evaluate the impact of a rapid screening strategy in improving nosocomial ESBL and CPE control in critically ill patients
Project leader: Stephan Jürgen Harbarth | University of Geneva

Understanding and modelling reservoirs, vehicles and transmission of ESBL-producing Enterobacteriaceae in the community and long term care facilities
Project leader: Stephan Jürgen Harbarth | University of Geneva

Aligning industry incentives with AMR control goals: Exploring the feasibility of an antibiotic susceptibility bonus for drugs to treat Gram-negative infection
Project leader: Stephan Jürgen Harbarth | University of Geneva

The molecular mechanism of outer membrane protein insertion by BamA and its role as a target for novel antibiotics
Project leader: Sebastian Hiller | University of Basel

Resistome in the pig farms: Comparison of the breeding and fattening units with a One Health approach **Project leader: Markus Hilty | University of Bern**

Tracking antibiotic resistance from environmental reservoirs to the food chain
Project leader: Jörg Hummerjohann | Agroscope

COMPASS study (COMputerized Antibiotic Stewardship Study)
Project leader: Benedikt Huttner | University of Geneva

A digital antimicrobial stewardship smartphone application to combat AMR: the AB-assistant **Project leader: Benedikt Huttner | University of Geneva**

Tolerance as a potential reservoir for the development of antibiotic resistance
Project leader: Urs Jenal | University of Basel

A new rapid and reliable bacterial phenotypic diagnostic technique detecting bacterial susceptibility to antibiotics using optical fibers
Project leader: Sandor Kasas | EPF Lausanne

Modelling the spread of antibiotic resistance genes between chicken and human
Project leader: Christophe Lacroix | ETH Zurich

Novel targeted bacteriophage endolysin-based approach for treatment of drug-resistant Staphylococcus aureus infections
Project leader: Martin Loessner | ETH Zurich

Potentials of incentive-based instruments to an animal-friendly reduction of antibiotics usage **Project leader: Stefan Mann | Agroscope**

Fast Assessment of antibiotic resistance in bacteria by using nanomechanical arrays **Project leader: Ernst Meyer | University of Basel**

A novel concept for veal calf production: "the outdoor veal calf"
Project leader: Mireille Meylan | University of Bern

Antibiofilm therapy using Local Application of Bacteriophages
Project leader: Thomas Moriarty | AO Research Institute

AntibioticScout: Online tool for antimicrobial stewardship in veterinary medicine
Project leader: Hanspeter Naegeli | University of Zurich

Rapid diagnostic tests for detection of antibiotic resistance in clinically-significant Gram-negative bacteria
Project leader: Patrice Nordmann | University of Fribourg

Risk of companion animal to human transmission of antimicrobial resistance during different types of animal infection
Project leader: Vincent Perreten | University of Bern

Ecosystem- and genome-guided antibiotic discovery
Project leader: Jörn Piel | ETH Zurich

Dynamics of transmission of polymyxin resistance genes in Enterobacteriaceae; from the environmental source to the patient
Project leader: Laurent Poirel | University of Fribourg

Escherichia coli ST131: a model for high-risk transmission dynamics of antimicrobial resistance **Project leader: Laurent Poirel | University of Fribourg**

Partnership against Biofilm-associated Expression, Acquisition and Transmission of AMR **Project leader: Qun Ren | EMPA**

Antimicrobial peptide dendrimers (AMPD) and bicyclic peptides (AMBP) as therapeutic agents against multidrug resistant bacteria
Project leader: Jean-Louis Reymond | University of Bern

Rapid diagnostics of blood stream infections using synthetic nanobodies
Project leader: Markus Seeger | University of Zurich

Single-Dose Versus 3-Day Cotrimoxazole Prophylaxis in Transurethral Resection or Greenlight Laser Vaporisation of the Prostate: A Pragmatic, Multicentre Randomised Placebo Controlled Non-Inferiority Trial
Project leader: Hans-Helge Seifert | University of Basel

Implementation of routine audit and feedback on the use of protected anti-Gram-negative antibiotics: a multicenter, randomized trial using segmented regression analysis of interrupted time series
Project leader: Laurence Senn | University of Lausanne

Intervention of antimicrobial resistance transfer into the food chain
Project leader: Xaver Sidler | University of Zurich

Transmission of ESBL-producing Enterobacteriaceae and their mobile genetic elements – identification of sources by whole genome sequencing
Project leader: Sarah Tschudin-Sutter | University of Basel

Piloting on-site interventions for reducing antimicrobial use in livestock farming in emerging economies **Project leader: Thomas Van Boeckel | ETH Zurich**

Fighting antimicrobial resistant infections by high-throughput discovery of biofilm-disrupting agents and mechanisms
Project leader: Jan-Willem Veening | University of Lausanne

Developing an evidence-based intervention for consumers to reduce the risk of multiple antimicrobial resistance transmission pathways
Project leader: Vivianne Visschers | FHNW

Comparative assessment of social-ecological resilience and transformability to limit AMR in one health systems
Project leader: Didier Wernli | University of Geneva

Publication details

Editors

Joachim Frey, President of the Steering Committee of NRP 72
Stéphane Praz, Head of Knowledge Transfer NRP 72 /
Leporis Communication, Zurich
In cooperation with the Steering Committee of NRP 72

Recommended citation style

Steering Committee of NRP 72 (2022): Programme summary
of the National Research Programme "Antimicrobial Resistance"
(NRP 72), Swiss National Science Foundation, Bern.



Antimicrobial Resistance
National Research Programme



**Swiss National
Science Foundation**

Design and layout

Binkert Partnerinnen AG, Zurich

Illustrations

Vaudeville Studios, Zurich

The respective research teams are responsible for the research results mentioned, the teams of authors for the thematic syntheses and their recommendations, and the Steering Committee for the programme summary; the opinions expressed do not necessarily agree with those of the Swiss National Science Foundation.

Steering Committee

Prof. Joachim Frey, Institute of Veterinary Bacteriology, Vetsuisse Faculty, University of Bern, Bern (President)
Prof. Peter Frey, Institute of Bioengineering, EPF Lausanne
Prof. Petra Gastmeier, Institute of Hygiene and Environmental Medicine, Charité – Universitätsmedizin Berlin, Germany
Prof. Herman Goossens, Laboratories of Clinical and Medical Microbiology, University of Antwerp, Belgium
Prof. Susanne Häußler, Department of Molecular Bacteriology, Helmholtz Centre for Infection Research, Braunschweig, Germany
Dr Jean-Yves Madec, French Agency for Food, Environmental and Health Safety (Anses), Lyon, France
Prof. José L. Martínez, Departamento de Biotecnología Microbiana, Centro Nacional de Biotecnología, Madrid, Spain
Prof. Dik Mevius, Faculty of Veterinary Medicine, Utrecht University, Wageningen Bioveterinary Research Lelystad, Netherlands
Dr Malcolm G. P. Page, Malcolm Page GmbH, Basel
Prof. Mathias Pletz, Institute of Infectious Diseases and Infection Control, Jena University Hospital, Germany

Delegate of Division IV of the National Research Council

Prof. Dr Nicolas Rodondi, Institute of Primary Health Care (BIHAM), University of Bern

Federal Representative

PD Dr Dagmar Heim, Head of Veterinary Medicinal Products and One Health sector, Federal Food Safety and Veterinary Office (FSVO), Bern

Programme Manager

Dr Barbara Flückiger Schwarzenbach, SNSF, Bern

Head of Knowledge Transfer

Stéphane Praz, Leporis Communication, Zurich

ISBN 978-3-907087-54-1

