



Portrait of the National Research Programme (NRP 72)

Antimicrobial Resistance



SWISS NATIONAL SCIENCE FOUNDATION

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What is an NRP?

National Research Programmes (NRP) provide scientifically substantiated solutions to urgent problems of national significance. They are approved by the Federal Council, last from 4 to 5 years and are funded with CHF 5 to 20 million. NRPs are problem-oriented; inter- and transdisciplinary; dedicated to achieving a defined, overall goal through coordination of individual research projects and groups and focused on the knowledge transfer of the results.

A call for innovation and targeted implementation. Science take note.

Antibiotic drugs are indispensable to modern medicine. But their effectiveness is under threat: more and more pathogens are becoming resistant to one or several antibiotics, and increasingly even to all available antibiotics. If this trend continues, we run the risk of not being able to treat bacterial infections in the foreseeable future. This would have grave consequences for patients and for society at large.

It is time to act. The political will to do so is there. In September 2016, the UN General Assembly declared antibiotic resistance to be a priority.

Many countries are planning measures or have already implemented them. Switzerland has launched its National Strategy on Antibiotic Resistance (StAR), which includes comprehensive efforts in the areas of human and animal medicine, agriculture and the environment.

Yet despite this commitment to act, in certain areas we lack the knowledge or appropriate means to effectively fight antimicrobial resistance. Consequently, although it is clear that we must reduce the use of antibiotics, the question is how we can achieve the necessary

behavioural changes in a way that is politically, socially and economically acceptable.

In addition, new drugs are urgently needed against resistant organisms. We also require faster diagnostic tools that enable targeted treatment of infections. Unfortunately, too little has been done in both these areas in recent years.

Finally, we need better understanding of the processes that lead to the development and spread of resistance. Such knowledge is a prerequisite for being able to selectively prevent the transfer of resistance genes between bacteria and across different ecosystems.

In view of these challenges and the persistent lack of approaches to solving them, science has a pivotal role to play. It must supply the knowledge that is critical to overcoming antimicrobial

resistance. NRP 72 aims to contribute to this goal. Together, practitioners of clinical and veterinary medicine, biologists and environmental scientists are tackling the many tasks associated with developing practical solution approaches in all the fields.

We realise that this is a very ambitious goal. The problem of resistance demands innovation and targeted implementation from us as researchers. Both require a comprehensive approach given the complexity of the problem. This is the “one health” approach. It recognises that the development and spread of antimicrobial resistance in humans, animals and the environment must be investigated across the board. Consequently, we are combining our forces and working together on projects in an interdisciplinary manner.

However, we do not wish to exchange the knowledge gained only among scientists. Rather, it should reach anyone involved in promoting the fight against antimicrobial resistance in practice. This includes those charged with implementing StAR as well as stakeholders in politics, business, public health and many other areas.

We are all working towards the same goal: securing the future of antibiotics as a cornerstone of modern medicine.



A handwritten signature in black ink, consisting of a stylized 'C' followed by a loop and a horizontal line.

Prof. Christoph Dehio
President of the Steering Committee
NRP 72

A comprehensive research approach to a multifaceted problem

The National Research Programme “Antimicrobial Resistance” (NRP 72) seeks new solutions to overcoming the problem of antibiotic resistance. To this end, it brings together research groups from different disciplines who are investigating various aspects of resistance.

Since the end of the last century, the world has faced a dramatic development: the increasing spread of antimicrobial resistance. More and more frequently, clinicians must deal with serious infections caused by pathogens that are resistant to all the antibacterial drugs available on the market.

Focus on applied research

To counter this development, the Swiss National Science Foundation (SNSF)

launched the National Research Programme “Antimicrobial Resistance” (NRP 72) on behalf of the Federal Council. This is the second NRP devoted to this topic. The first, NRP 49, was conducted over the period 2001–2006. Its pioneering achievements led to the creation of the Swiss Centre for Antibiotic Resistance (Anresis), which monitors and analyses trends in resistance. Now, NRP 72 is focusing more closely on applied research. One reason for this shift in

emphasis is the major advances achieved in recent years in the field of gene sequencing and the biochemical analysis of cellular processes. These advances are the foundations of new approaches to research and solutions.

Different disciplines contribute to solutions

The spread of antibiotic resistance among humans cannot be dissociated from the presence of resistant bacteria

and resistance-encoding genes in animals, the food chain and the environment. Consequently, it is essential to take all these areas into account. NRP 72 does this through a comprehensive, cross-disciplinary “one health” approach. The research projects are divided into three modules that investigate various aspects of resistance:

Module 1

Development and spread of resistance

Many aspects of the development and spread of resistant bacteria are still unknown. To understand the complex processes involved, we need a research approach that combines human medicine, veterinary medicine, biology and environmental sciences. The results of such research will help us to disrupt the processes through which resistant bacteria are able to spread.

Module 2

New drugs and faster diagnostic techniques

To fight resistant bacteria, both human and veterinary medicine urgently need new antibiotic drugs. Academic research can make a major contribution to their development. Furthermore, faster diagnostic tests are important to identify resistant strains quickly and treat people and animals adequately.

Module 3

Optimised use of antibiotics

When antibiotics are used excessively or wrongly, resistance is more likely to develop. New decision-making tools and operational processes will help medical and veterinary doctors as well as farmers to use antibiotics more selectively.

Development and spread of resistance

Projects:

How rapidly bacteria exchange information

Prof. Sebastian Bonhoeffer

Phages and the spread of resistance in different ecosystems

Dr. Elena Gomez Sanz

Resistance on lettuce plants

Dr. David Drissner

Sources of resistant germs in the city of Basel

Dr. Sarah Tschudin Sutter

Antibiotic Resistance from waste water treatment facilities in Swiss streams and rivers

Dr. Helmut Bürgmann

How germs transfer resistance to each other

Prof. Melanie Blokesch

Transfer of resistance to polymyxin antibiotics from the environment to humans

Dr. Laurent Poirel

How to quickly identify sources and distribution pathways of resistance

Prof. Andrea Endimiani

The genetic relationship between pathogens reveals the routes by which they spread

Prof. Adrian Egli

Antibiotic resistance on Swiss pig farms

PD Dr. Markus Hilty

How bacteria outsmart antibiotics in their sleep

Prof. Urs Jenal

Reducing the transfer of resistance between chickens and humans

Prof. Christophe Lacroix

How rapidly bacteria exchange information

Bacteria exchange plasmids that contain genetic information involved in the development of resistance. We are researching their role and analysing factors that accelerate plasmid exchange.

One of the ways in which antibiotic resistance spreads is by bacteria transferring genetic material among themselves. This material includes plasmids. In order to clarify the role played by plasmids, we first use bioinformatic methods to estimate how often different types of bacteria exchange plasmids. We also measure this transfer frequency in an animal model using mouse gut bacteria under the influence of different factors such as inflammation or low concentrations of antibiotic. We then record the transfer frequency of plasmids in bacterial cultures in the laboratory. We use all the recorded data to develop mathematical models that calculate the effect of different factors on the transfer rate of plasmids and thus on the transfer of resistance.

Prof. Sebastian Bonhoeffer

ETH Zurich, Department of Environmental Systems Science

Phages and the spread of resistance in different ecosystems

Some resistance determinants to antibiotics seem to develop and spread in natural eco-systems, which are later transferred to human related systems. We clarify the role that bacterial viruses, so-called bacteriophages, play in these processes.

The use of antimicrobials by humans is often named as the sole reason for the emergence and rise of antimicrobial resistance. However, genes that make bacteria resistant to antibiotics can also be found in virgin soils and bodies of water. It can be assumed that the origin of some of the resistances encountered in human medicine lies in these eco-systems. We investigate the resistance load in soils and bodies of water and how resistance is transferred between micro-organisms living in them. Our main focus is on bacterial viruses, so-called bacteriophages. They play an important role in the exchange of genetic material between bacteria, and they could also be responsible for the transfer of resistance genes between different eco-systems.

Dr. Elena Gomez Sanz

ETH Zurich, Institute of Food Science and Nutrition

Resistance on lettuce plants

Antibiotic-resistant germs are repeatedly found on lettuce. We identify the sources from which they are transferred to the plants during cultivation.

Antibiotic-resistant bacteria occur in the environment, in soil, bodies of surface water and organic fertilisers used in agriculture. They are presumed to pass from these sources to humans via plant-based food. However, little is known about how these bacteria are transferred from the environment to commercially grown plants. We are studying this aspect in lettuce cultivation and determining the sources from which resistant bacteria are transferred to the plants. We are investigating soil, irrigation water and fertilisers used during growth up to the point the plants are harvested. We are analysing which bacteria are transferred from which sources and in what quantities, as well as which forms of resistance persist until harvesting. Our study looks at both field and greenhouse cultivation.

Dr. David Drissner

Agroscope Wädenswil, Institute for Food Sciences

Sources of resistant germs in the city of Basel

We are using samples obtained from the Basel urban region to investigate the role played by different sources such as hospitals, foodstuffs and waste water in the spread of antibiotic-resistant bacteria.

The most common bacterial pathogens in humans include several species of the family of Enterobacteriaceae. Many of them have now become resistant to antibiotics. They occur in hospitals and also on food and in waste water. We are studying the contribution made by each of these sources to the spread of resistant Enterobacteriaceae. To do this we are analysing several hundred bacterial strains found in patients at University Hospital Basel, on food obtained from retail outlets and in waste water from the city of Basel. We are using molecular genetic methods to determine which bacteria are genetically related. By doing so we can identify the ways in which individual bacterial strains spread and highlight the role played by the different sources.

Dr. Sarah Tschudin Sutter

University Hospital of Basel, Department of Infectious Diseases & Hospital Epidemiology

Many resistant bacterial strains are found in hospitals. Sarah Tschudin Sutter (right) wants to know whether they are related to organisms from sources outside hospital.





Helmut Bürgmann uses Niskin bottles to take water samples at different depths.

Antibiotic Resistance from waste water treatment facilities in Swiss streams and rivers

Antibiotic-resistant bacteria pass into watercourses when waste water is discharged. We are investigating how this resistance behaves and where humans come into contact with it.

Normal waste water treatment facilities do not remove all resistant bacteria from waste water. We are looking at which bacteria, bearing which types of resistance, pass into Swiss streams and rivers in this way and where they can subsequently be found. We are paying special attention to bacteria in aquatic animals, sediments and so-called biofilms: layers of bacteria on the surface of water and soil. We are also recording the distances over which resistance is transported and how robust it is. This information will enable us to develop models to predict the resistance burden of flowing waterways along their courses. The intention is to identify places in which humans could come into contact with resistance from waste water treatment facilities.

Dr. Helmut Bürgmann
Eawag, Kastanienbaum

How germs transfer resistance to each other

Dead bacteria release DNA molecules that other bacteria can incorporate into their own genetic material. We are investigating the way in which, during this process, they pass on genetic information that leads to the development of antibiotic resistance.

Antibiotic resistance is spread not only by multiplying resistant bacteria, but also by bacteria exchanging genetic material between themselves. An important role in this process is played by the ability of bacteria to incorporate free DNA present in a medium in which they are immersed. We are investigating this mechanism in bacteria from the species *Acinetobacter baumannii* with the aim of finding out how the mechanism contributes to the development of resistance. Resistant strains of these bacteria are found repeatedly, particularly in hospitals. At this stage it is often no longer possible to treat them due to multi-resistance. In a second step we are analysing how the studied mechanism contributes to the spread of resistance when bacteria come into contact with antibiotics.

Prof. Melanie Blokesch
EPF Lausanne, Global Health Institute

Transfer of resistance to polymyxin antibiotics from the environment to humans

Resistance to the polymyxin group of antibiotics is increasing. Some of the determinants of this resistance are transmitted from environmental bacteria to human pathogens. We are investigating the nature, origin, and mode of transmission of the determinants of polymyxin resistance from environmental sources to pathogens.

Polymyxins are antibiotics of last resort in human medicine that are also frequently used in veterinary medicine. An increasing number of pathogens is becoming resistant to polymyxins, including many *Escherichia coli* and *Klebsiella pneumoniae* isolates. We have identified such strains and are now investigating the mechanisms responsible for their resistance to polymyxins. Our research takes into account resistance resulting from mutations in the bacteria's chromosome as well as resistance arising from the exchange of genetic material with other bacteria. We study resistance mechanisms in bacterial isolates recovered from the environment, humans or animals. Comparing these samples yields information about which mechanisms are spreading and the way this actually happens.

Dr. Laurent Poirel

University of Fribourg, Medical and Molecular Microbiology Unit

How to quickly identify sources and distribution pathways of resistance

We are comparing genetic data from antibiotic-resistant enterobacteria obtained from patients, foodstuffs, animals and the environment. This will allow us to identify how individual resistance patterns spread. Our goal is to develop the basis for detailed and timely monitoring of disease outbreaks.

Thanks to new sequencing methods, it is now possible to conduct comprehensive genetic analyses of bacteria, both in terms of their unchangeable genetic information and mobile genetic elements that do not belong to the chromosome. We are doing this with over 1,600 samples of multidrug-resistant enterobacteria from patients, foodstuffs, farm animals, wildlife and wastewater. We are linking all the data with each other and with epidemiological data on affected patients. Thus, we will gain insights into the spread of individual resistance patterns across the human, food chain, animal and environmental settings. Our work serves to develop and test a system to very quickly analyse sources of novel antibiotic resistance genes, the genetic background of promiscuous bacterial clones, and their pathways of transmission.

Prof. Andrea Endimiani

University of Bern, Institute for Infectious Diseases

The genetic relationship between pathogens reveals the routes by which they spread

We are determining the genetic proximity of multiresistant bacteria from several human and veterinary hospitals. This will show how closely related they are and will enable researchers to understand the routes by which they spread.

The routes by which multiresistant bacteria spread are highly complex and involve humans, animals and the environment. However, they can be uncovered by performing a genetic comparison to determine how individual pathogens are related. The greater the similarity between two bacteria, the more recently they were transmitted. We are developing a nationwide database that will make it possible to estimate timing and geographical routes in the spread of multiresistant pathogens. We are doing this by networking and standardising data from several human and veterinary hospitals. The database will analyse a diverse range of pathogens and produce a visual depiction of how they are related, thus helping to generate valuable findings about the outbreak of disease in hospitals and among the population at large.

Prof. Adrian Egli

University Hospital of Basel, Department of Biomedicine

Antibiotic resistance on Swiss pig farms

We are investigating how many and which types of antibiotic resistance occur in animals and people on Swiss pig farms and in the environment. Our work will also highlight the key risk factors in the spread of resistance, which could in turn provide a basis for preventive measures.

We are investigating the occurrence and transmission routes of antibiotic resistance on Swiss pig farms. We are testing samples from farmers, their animals and the environmental area around the farms for resistance. Animals will be tested at birth, at five weeks of age and shortly before slaughtering. The aim of this repeat testing is to establish whether the number and types of resistance found in animals changes during their life cycle. We are describing all the resistance genes, or the so-called resistome, in all samples. This will enable us to compare the samples and identify associations that extend beyond animals, people and the environment. By combining this with information on how the animals are kept, which we will obtain by means of a questionnaire, we will be able to identify risk factors.

PD Dr. Markus Hilty

University of Bern, Institute for Infectious Diseases

How bacteria outsmart antibiotics in their sleep

Some bacteria can enter a resting state that makes them insensitive to antibiotics. Our goal is to find out how this state works, which role it plays in antibiotic therapy and whether it facilitates the emergence of antibiotic resistance.

Bacterial pathogens can survive contact with antibiotics by modifying their DNA to develop resistance. But there is an alternative way to survive antibiotic exposure, known as antibiotic tolerance. Tolerant bacteria survive exposure to antimicrobial drugs by switching their cell metabolism into a resting state thereby eliminating their susceptibility. The molecular and cellular basis of this condition is largely unknown. We are investigating these processes in the bacterium *Pseudomonas aeruginosa*, a life-threatening human pathogen that is difficult to treat. In addition to uncovering the actual tolerance mechanisms, we are also investigating if and how they are linked to the development of antibiotic resistance.

Prof. Urs Jenal
University of Basel, Biozentrum

Reducing the transfer of resistance between chickens and humans

We show how antimicrobial resistance spreads in the intestines of poultry and humans and how these two hosts are linked in the development of resistant bacteria. Our work creates a basis for measures to reduce the development of resistance stemming from chicken production and meat consumption.

We are investigating how bacteria in the intestines of poultry become resistant and how this resistance is then passed on to microbes, including pathogens, in the human intestine. To this end, we will first conduct an animal study to determine which bacterial strains are particularly active in exchanging resistance genes. After that, we will analyse the capacity of these strains to transfer genetic material to other bacterial species. In subsequent steps, we investigate the exact mechanisms of this gene transfer process in the laboratory, first in a model of poultry intestine, then in a model of the human intestine. Finally, we will test the findings and resistant bacteria in an animal study with poultry.

Prof. Christophe Lacroix
ETH Zurich, Laboratory of Food Biotechnology



Christophe Lacroix uses a laboratory model to imitate the microbial composition and processes of poultry intestines.

New drugs and faster diagnostic techniques

Projects:

Improving established antibiotics

Prof. Erik Christian Böttger

Identifying resistance with glass fibres

Prof. Giovanni Dietler

Antibacterial weapons from the phyllosphere

Prof. Jörn Piel

Smaller means faster: diagnostics on a microchip

Prof. Petra Dittrich

Exploiting the natural enemies of bacteria

Prof. Martin Loessner

Getting inside the protective shield of bacteria

Prof. Sebastian Hiller

Artificial alternative to an important natural substance

Prof. Jean-Louis Reymond

A pathogen's proteins show whether it is resistant

Prof. Dirk Bumann

Expanding successful diagnostic methods

Prof. Patrice Nordmann

Specific antibodies capture germs

Prof. Markus Seeger

Using nanosensors to track down resistance genes

Prof. Ernst Meyer

Improving established antibiotics

The aim of this project is to develop new, highly potent antibiotics based on the aminoglycoside compound class.

The aminoglycosides are a class of highly potent antibiotics that are active against numerous bacterial pathogens such as enterobacteria, staphylococci and tuberculosis bacteria. Aminoglycosides are used predominantly in the hospital setting to treat serious infectious diseases. In the past decades, increasing resistance to these antibiotics has developed, and their use is additionally limited by considerable side effects. Taking recent findings on the complex mechanisms of action and resistance of aminoglycosides into account, our aim is to further develop this substance class.

Prof. Erik Christian Böttger

University of Zurich, Institute of Medical Microbiology

Identifying resistance with glass fibres

We are developing a new test instrument that identifies bacterial resistance by means of glass fibres and a laser beam. Our aim is to shorten the time between a patient being admitted and the start of appropriate therapy from the current 24 to 10 hours.

Our method is based on the use of hair-thin glass fibres to which the live bacteria being tested are fixed. Their movements are transmitted to the fibres, the vibrations of which are recorded by a laser and visualised on a computer screen. If a bacterium is susceptible to an added antibiotic, it dies and the glass fibre stops moving after about 10 to 20 minutes. If, on the other hand, the laser is still detecting movement after this time has elapsed, then the bacterium is resistant to the antibiotic that has been administered. The advantages of our method compared with conventional tests are the rapid availability of the result and the possibility of testing different antibiotics in parallel by using several glass fibres.

Prof. Giovanni Dietler

EPF Lausanne, Laboratory of Physics of Living Matter

Antibacterial weapons from the phyllosphere

A diverse microcosm, called the phyllosphere, exists on the surfaces of leaves. It is here that bacteria wage war on each other with antibiotics. We are systematically analysing these organisms and substances to discover new active substances.

Today's antibiotics come mainly from naturally occurring bacterial substances isolated from soil samples. However, there exist numerous additional microorganisms with major potential as drug sources that has as yet barely been tapped into. These include bacteria found on leaf surfaces. Our decision to study them was motivated by well-documented evidence that they produce antibiotics as a defence against hostile bacteria. Using state-of-the-art methods of genetic analysis and bioinformatics, we plan to identify bacteria that show considerable promise for the discovery of antibiotic substances. We will isolate and test these substances chemically and pharmacologically with the goal of making especially promising substances available for the development of medicines.

Prof. Jörn Piel

ETH Zurich, Institute of Microbiology

Using a fluorescence microscope, Petra Dittrich determines exactly what is happening on the microchip.



Smaller means faster: diagnostics on a microchip

We want to use a novel test to make the diagnosis of antibiotic resistance much faster. We are developing a miniaturised process that will directly analyse individual germs on a microchip.

It currently takes hours or even days to determine whether a germ is resistant to an antibiotic. That's often too long when doctors need to take decisions about treatments. We are developing a new diagnostic method that will deliver reliable results within a few hours. We want to determine not only the type of resistance displayed by a pathogen but also what concentration of what antibiotic is needed to stop the infection. At the heart of our device is a microchip on which minute quantities of germs can be fixed and analysed. The use of such small sample quantities substantially reduces the time needed for analysis compared with conventional methods. We are testing the reliability of our device in the routine clinical setting.

Prof. Petra Dittrich

ETH Zurich, Bioanalytics Group

Exploiting the natural enemies of bacteria

Bacteriophages kill bacteria. We are investigating how the bacteriophages' weapons can be used as new therapeutics to combat local infections within the body.

Bacteria have natural enemies named bacteriophages. They use the bacteria as a host for the purpose of multiplication. When they leave the bacteria, they degrade the bacterial cell wall using specific enzymes, known as endolysins, causing the bacteria to die. We aim to develop therapeutics containing endolysins that are capable of destroying pathogenic bacteria. For them to be effective against local infections within the body, e.g. cases of inflammation of the bones or heart, they need to reach the infected sites. To achieve this, we put special target markers on endolysins. These "biological zip codes" guide them directly to the affected regions in the body.

Prof. Martin Loessner

ETH Zurich, Laboratory of Food Microbiology

Getting inside the protective shield of bacteria

Many particularly dangerous bacteria are protected by an outer membrane. We want to understand the mechanism by which this membrane develops in order to find targets for new active substances.

Infections by so-called Gram-negative antibiotic-resistant bacteria are difficult to treat because these bacteria are protected by two membranes. Yet there are points in the outer membrane that are open to attack by active substances. We are characterizing one of these points, the protein BamA. BamA controls the process of incorporating other proteins into the membrane. If BamA is knocked out, this is fatal for the bacterium. We are studying the function of BamA and the incorporation of proteins at the atomic level, using NMR spectroscopy and X-ray crystallography. This makes the interactions between BamA and other molecules visible. In this way we can gain a better understanding of the mechanisms and look for active substances that interrupt them.

Prof. Sebastian Hiller

University of Basel, Biozentrum

Artificial alternative to an important natural substance

We are looking for an alternative to the important natural antibiotic colistin. With this in mind we are systematically exploring related structures by chemically synthesising those that do not occur naturally.

When nothing else works, maybe colistin will. Nowadays this antimicrobial peptide of natural origin is used as the last resort against many multiresistant germs. Yet it can have considerable side effects, and there are now bacteria that are resistant to it. Other peptides offer particular promise in the search for alternatives to this important substance. We have already discovered some that are active against multiresistant bacteria by systematically investigating peptides related to colistin that do not occur naturally. They have never been studied before because they are not natural substances. We are now optimising these artificial peptides, investigating their mechanism of action and assessing which might be useful for medical purposes.

Prof. Jean-Louis Reymond

University of Bern, Department of Chemistry and Biochemistry



First, Jean-Louis Reymond obtains the peptides in solution.
In the next step, they are freeze dried to get them in powder form.

A pathogen's proteins show whether it is resistant

We are developing a diagnostic method to identify resistances based on protein abundance in pathogens. The analytical process we implement should deliver informative results quickly.

Broad-spectrum antibiotics from the cephalosporin group are generally effective against pathogenic enterobacteria. However, as an increasing number of pathogens are becoming resistant to these antibiotics the use of drugs of last resort is growing – frequently without full knowledge of the resistance situation. We are developing a diagnostic method capable of determining resistances in a matter of hours. It analyses the protein composition of bacteria in samples taken directly from patients, thus eliminating the need for the time-consuming process of microbial cultivation that is standard practice today. To ensure that our project produces meaningful results, we are investigating in a first step which proteins in enterobacteria are responsible for resistances.

Prof. Dirk Bumann
University of Basel, Biozentrum

Expanding successful diagnostic methods

Taking successful diagnostic methods as a basis, we are developing new tests for further resistance traits. These should deliver results in less than three hours and require only simple laboratory equipment.

Molecular biology tests have become established in everyday clinical practice because they recognise many resistance genes in pathogens. Taking successful methods as a basis, we intend to develop further tests that can detect additional known resistance traits, but are also able to detect new resistance variants. The tests are based on biochemical, immunological and rapid culture methods, depending on the molecular property that is responsible for resistance and is therefore to be identified. We are focusing on difficult-to-treat multi-resistant bacteria, in particular hospital-acquired bacterial species such as Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. The tests are expected to deliver results in less than three hours and require only simple laboratory equipment.

Prof. Patrice Nordmann
University of Fribourg, Medical and Molecular Microbiology Unit

Specific antibodies capture germs

We are developing a rapid test for three important bacterial pathogens. The test is based on specific antibody fragments that bind directly to and capture pathogens in blood samples.

It can take several days to detect the pathogen responsible for blood poisoning (sepsis). A lot of time is lost in current tests due to the need to replicate bacteria. We are working on a process that is substantially faster because it can isolate pathogens straight from blood samples. Our method uses synthetic antibody fragments – what are known as sybodies – that bind to pathogens. To do so, they need a structure that is adapted to the bacterial species in question. As a first step, we are therefore developing sybodies that will specifically dock to all clinically relevant strains of the *E. coli*, *K. pneumoniae* and *P. aeruginosa* bacteria. This will provide a basis for developing a rapid test capable of quickly analysing these pathogens by counting individual cells and testing them for antibiotic resistance.

Prof. Markus Seeger

University of Zurich, Institute of Medical Microbiology

Using nanosensors to track down resistance genes

Antibiotic-resistant bacteria display distinct genetic sequences, depending on the resistance. We are developing nanosensors that are specifically capable of identifying these different sequences so that pathogens can be quickly and reliably tested for resistance.

We are developing a nanotechnology-based diagnostic method that can recognise antibiotic resistance in a very short time. Our technology centres around sensors coated with various biomarkers. Each of these markers only binds to certain genetic sequences, such as those responsible for certain resistances. When a bacterial sample containing the relevant sequence comes into contact with a nanosensor, the sensor bends – only very slightly, but still measurably. We will initially use the method to identify the genetic sequences underlying different resistances. This will deliver a basis for assessing whether the markers reliably recognise the relevant resistances in patient samples.

Prof. Ernst Meyer

University of Basel, Department of Physics

Optimised use of antibiotics

Projects:

Feedback culture and the rational use of antibiotics in the hospital setting

Dr. Laurence Senn

Learning from claim data

Prof. Heiner C. Bucher

Using computers to improve prescription practices

Dr. Benedikt Huttner

Online help for veterinarians

Prof. Hanspeter Naegeli

Providing the right incentives

Dr. Stefan Mann

The “outdoor” calf – a new concept for calf fattening

Prof. Mireille Meylan

An algorithm to improve the diagnosis of pneumonia

Dr. Noémie Boillat Blanco

Faster screening benefits patients and cuts costs

Prof. Stephan Harbarth

Detecting excessive antibiotic use in urology – less is more

Prof. Andreas Widmer

Ensuring safe food handling

Dr. Vivianne Visschers

Feedback culture and the rational use of antibiotics in the hospital setting

We are carrying out a study in nine hospitals to determine whether doctors use antibiotics more specifically if infectious diseases specialists evaluate their prescribing habits regularly and provide them with feedback.

Inappropriate prescribing of antibiotics can promote the development of resistance. We want to make prescribing doctors more aware of the need to use these medicines responsibly. To this end, we are developing a programme in which training is provided by infectious diseases specialists. They also review the doctors' prescribing habits on a weekly basis and discuss their findings with them. We are performing this intervention in a number of departments at nine hospitals in the French-speaking part of Switzerland. We have divided the departments randomly into two groups: the intervention takes place in one group, but not in the other. This allows us to check the efficacy of our programme.

Dr. Laurence Senn

Lausanne University Hospital, Service of Hospital Preventive Medicine

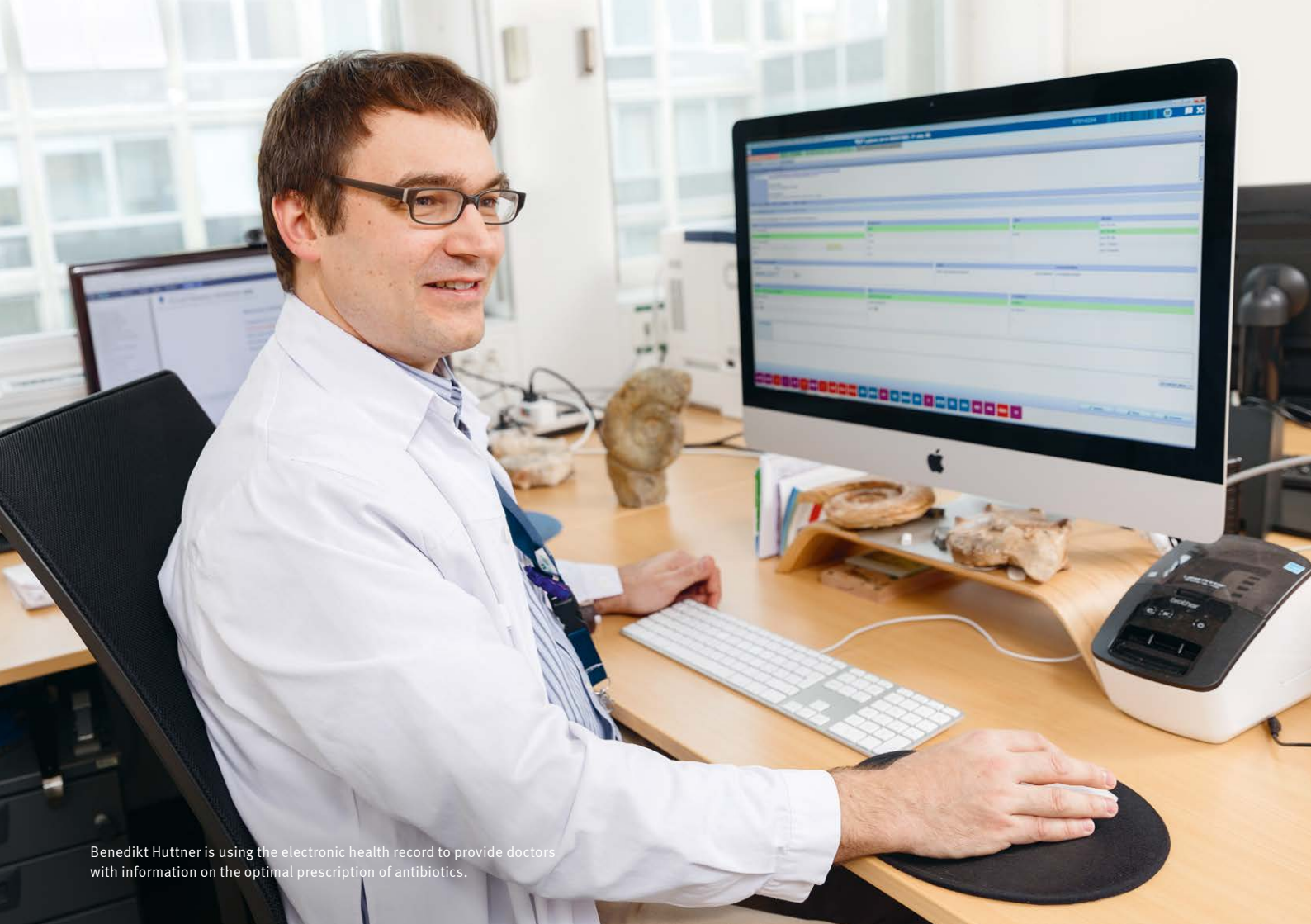
Learning from claim data

We are using claim data from health insurance providers to regularly inform general practitioners about their use of antibiotics. We are testing whether, in conjunction with information about local resistance development, this can improve prescribing habits.

General practitioners (GPs) often prescribe antibiotics indiscriminately for respiratory and urinary tract infections. We want to encourage them to use antibiotics more cautiously. To do this we are using the claim data from the three biggest health insurances (3.8 million insureds, or 40% of the Swiss population) to produce an ongoing evaluation of GPs' prescribing habits. We provide nearly 2,500 GPs with regular feedback on this as well as with information on the development of resistance in their catchment area. We also provide them with guidelines for treating respiratory and urinary tract infections. We then use the data from the health insurances to analyse the impact of this intervention. All the data are anonymous; we do not know the names of any of the doctors or patients.

Prof. Heiner C. Bucher

University Hospital of Basel, Institute for Clinical Epidemiology and Biostatistics



Benedikt Huttner is using the electronic health record to provide doctors with information on the optimal prescription of antibiotics.

Using computers to improve prescription practices

We are integrating a tool directly into the electronic health record to give hospital doctors feedback on the way they prescribe antibiotics. This system is being trialled in various hospitals.

Prescribing antibiotics frequently poses problems in practice, since patients don't always receive the right dosage of the right antibiotic for the right period of time. This promotes the emergence and spread of antibiotic resistance. We are developing a system designed to help doctors to use antibiotics more appropriately. Under COMPASS (COMPuterized Antibiotic Stewardship Study), doctors in three Swiss hospitals will receive tips on the use of antibiotics that are integrated directly into electronic health record. They will also be given regular feedback on their use of antibiotics. Parallel to this, we will collect data on the antimicrobial prescription practices of a control group which is not using the system so that we can monitor the latter's effectiveness.

Dr. Benedikt Huttner

University of Geneva Hospitals, Division of Infectious Diseases

Online support for veterinarians

We are launching an online platform for veterinarians that combines practical recommendations on antibiotics and a resistance reporting system. We will conduct three trials to determine whether this optimises and reduces the use of antibiotics.

Antibiotics are not always used optimally in the veterinary sector, whether for livestock or pets. This prompted us to develop an online platform as a support tool to support veterinarians use them more selectively. In addition to providing simple-to-adopt recommendations, the platform also offers an opportunity to give feedback if a treatment proves ineffective. This not only facilitates efforts to monitor the resistance situation, it also helps to improve recommendations. In order to verify the effectiveness of this tool, we will conduct two trials over a period of three years to collect data on changes in the use of antibiotics at university veterinary hospitals and private practices. We will also carry out a broad survey of Switzerland's veterinary community.

Prof. Hanspeter Naegeli

University of Zurich, Vetsuisse Faculty, Institute of Veterinary Pharmacology and Toxicology

Providing the right incentives

Positive incentives are crucial for reducing antibiotic use in the agricultural sector. We wish to establish how effective and broadly accepted incentive systems could be constructed.

The Swiss government's antibiotic resistance strategy (StAR) wants to reduce the use of antibiotics in agriculture. New incentive systems are also to be introduced to bring about a change in behaviour. We are investigating the options for incentive-based tools. Our study relies primarily on surveys conducted among veterinarians and farmers. In an initial phase, we will examine how antibiotics are being used today. Working in conjunction with veterinary practitioners, we will then develop several financial incentive methods designed to reduce the use of antibiotics. Then we will carry out a further survey to ascertain what level of acceptance these options have achieved among the farming community. We will use our findings to prepare recommendations for the relevant federal offices.

Dr. Stefan Mann
Agroscope Reckenholz-Tänikon

The “outdoor” calf – a new concept for calf fattening

We are testing a new management concept for calf fattening that sets out to halve antibiotic use. In this concept the calves grow up outdoors, with shelters and a covered exercise area.

In calf fattening operations, young animals from several herds of origin are often gathered to large groups. As a result, they pass on germs to each other that cause a large number of diseases, resulting in the use of large quantities of antimicrobial drugs. We are developing a new management concept for calves called the “outdoor calf”. The animals live outdoors, initially in individual igloos that enable them to be quarantined on arrival at the fattening centre. They are later kept in small groups with igloos and a bedded and sheltered outdoor area. This exposes them to fewer pathogens and they fall ill less often. We will test this concept in 20 herds, comparing the diseases that occur and antimicrobial use with 20 herds using traditional methods in the neighbourhood.

Prof. Mireille Meylan
University of Bern, Vetsuisse Faculty, Clinic for Ruminants

Healthy calves need fewer antibiotics.
Mireille Meylan visits a test facility with an
interspersed run.



Noemie Boillat Blanco uses a small portable ultrasound device as part of a new Algorithm to diagnose pneumonia.



An algorithm to improve the diagnosis of pneumonia

Current tests do not allow GPs to determine with sufficient accuracy whether a patient has pneumonia requiring antibiotic therapy. We are increasing the precision of diagnosis by combining two new diagnostic tests with an algorithm.

General practitioners too often prescribe antibiotics for acute respiratory tract infections because they cannot distinguish between bacterial pneumonia and non-bacterial infections. In order to improve diagnosis we are developing a procedure that combines ultrasound examination of the lungs with a procalcitonin test helping in differentiating between bacterial and viral infections. However, since each method on its own produces too many unreliable diagnoses, we are combining their results with an algorithm to increase diagnostic precision. In our study, several general practitioners are using this strategy, and we are comparing the amount of antibiotics they prescribe and the therapeutic outcomes with those of a comparator group who are not using the strategy.

Dr. Noémie Boillat Blanco

Lausanne University Hospital, Infectious Diseases Service

Faster screening benefits patients and cuts costs

We are testing a new strategy for screening carriers of multi-resistant gut bacteria in hospitals. This strategy will accelerate decisions on patients' treatment and on whether or not they need to be put into isolation.

Gut bacteria that are resistant to a large number of antibiotics due to their ability to produce special antibiotic-degrading enzymes such as ESBL and/or carbapenemases cause a substantial financial burden for hospitals. Affected patients are often identified too late or kept in isolation too long due to false alerts. We are therefore developing a faster screening strategy using the LAMP test pretested at the University of Geneva Hospitals, which is capable of rapidly identifying the most common multi-resistant gut bacteria. The LAMP test is supplemented by a new molecular test that specifically identifies the virulent, antibiotic-resistant *E. coli* strain ST 131. To assess its effectiveness, we will test the strategy over a period of 12 months and compare the results with conventional screening.

Prof. Stephan Harbarth

University of Geneva, Department of Internal Medicine Specialties

Detecting excessive antibiotic use in urology – less is more

Antibiotics are frequently used in urology. However, using them less would reduce the development of antibiotic resistance. We are therefore comparing a single prophylactic dose of antibiotics following urological surgery with the current clinical practice of three days or more.

We are conducting a questionnaire-based pilot study of real-life prophylactic use of antibiotics in two common prostate operations. Around a quarter of urologists comply with European guidelines for transurethral resection (trimming away diseased tissue) and GreenLight Laser PVP (vaporisation of diseased tissue). We will then divide patients into two groups as part of a randomised prospective study. The first group will receive a single prophylactic dose as prescribed by the guidelines, whereas the second will receive a three-day prophylactic course of the type that is very commonly used in practice. This will enable us to compare the effect of each type of prophylaxis on postoperative infection, antibiotic-associated side effects and the development of antimicrobial resistance.

Prof. Andreas Widmer

University Hospital of Basel, Institute for Clinical Epidemiology and Biostatistics

Ensuring safe food handling

We are investigating the transmission risks of antibiotic-resistant bacteria between animals and humans in Switzerland. In addition, we are testing intervention approaches intended to sensitise consumers to handle their food safely.

Consumers are exposed to antibiotic-resistant bacteria through animal contact (e.g. through food consumption and by taking care of pets). We are developing intervention approaches intended to sensitise consumers to the need to act safely. As a first step, we are creating a risk map showing the transmission routes between animals and humans. We will then interview end-consumers, veterinarians and farmers to reveal their perceptions of the risks in question. This will enable us to identify existing knowledge gaps and highlight the areas, where an intervention is needed. Finally, we will test how various intervention approaches influence consumers' food handling.

Dr. Vivianne Visschers

University of Applied Sciences and Arts Northwestern Switzerland,
School of Applied Psychology

JPIAMR: Cross-border research

In order to coordinate international research into resistance and collaborate on the corresponding projects, 26 countries are taking part in the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR). NRP 72 finances Swiss research teams participating in JPIAMR projects that are pursuing the same goals.

Projets:

Resistant germs in long-term care and in the home

Prof. Stephan Harbarth

How resistance transfers from pets to humans

Prof. Vincent Perreten

The secret of ST131's success

Dr. Laurent Poirel

How bacteria unify to protect against antibiotics

Dr. Qun Ren Zulian

Reconciling the profit motive with sustainable use of antibiotics

Prof. Stephan Harbarth

Reducing antibiotic use in pig production in Thailand

Dr. Thomas Van Boeckel

Reducing antibiotic resistance in slurry

Dr. David Drissner

Making healthcare systems resilient to antimicrobial resistance

Dr. Didier Wernli

AB-Assistant: improving antimicrobial prescribing with a smartphone app

Dr. Benedikt Huttner

Resistant germs in long-term care and in the home

We are studying the transmission of resistant enterobacteria in long-term care and in the home. Together with the findings from other research groups we aim to provide a comprehensive picture of the ways in which these pathogens spread.

Multi-resistant intestinal microbes of the enterobacteria family are spreading rapidly all across the globe. Switzerland has also seen an increase of new infections. The pathogens can be found in hospitals, homes, on food and in the environment. Working together with research groups from six European countries, we seek to explain the precise ways in which they spread. Within the framework of our subproject, we are investigating how resistance is transferred within long-term care institutions and private homes. We are analysing various strains of enterobacteria, as well as mobile genetic elements that are exchanged between bacteria and play an important role in the formation of resistance.

Prof. Stephan Harbarth

University of Geneva, Department of Internal Medicine Specialties

How resistance transfers from pets to humans

Close contact between pets and their owners creates more favourable conditions for the transfer of antibiotic resistance. An international research project is investigating which infections and situations pose the greatest risks.

With increasing frequency, humans are contracting infections from antibiotic-resistant pathogens transferred from their pets. A consortium of research groups from four European countries and Canada is seeking to explain the circumstances that make the exchange of pathogens and resistance genes between humans and animals more likely. Our team is assisting in an advisory role, as well as carrying out molecular analysis of resistance genes. The project focuses on the processes during the acute stage of an infection, since the relevant bacteria and resistance genes increase greatly during this time. By studying pet owners and their animals over a longer period, it is possible to determine the transfer risks of a range of infections at different points during the course of the infection.

Prof. Vincent Perreten

University of Bern, Vetsuisse Faculty, Institute of Veterinary Bacteriology

The secret of ST131's success

There is a type of *Escherichia coli* bacteria occurring frequently around the world that is resistant to multiple groups of antibiotics. We are investigating how this pathogen acquires and transmits resistance.

Most urinary tract infections and cases of blood poisoning are caused by *E. coli* bacteria. Strains resistant to multiple antibiotics are occurring increasingly worldwide, especially one type named ST131. In a project comprising six research groups from five countries, we are investigating why the infectious potential of ST131 is so high, and how it acquires resistance. Our team explores the genetic processes by which *E. coli* integrates specific genes from other bacteria into its own genome thereby expanding its resistance. In earlier studies we have already identified a genetic element (ISEcp1) that plays an important role in this transfer. We are now analysing the mechanisms that are responsible for the observed processes *in vitro*.

Dr. Laurent Poirel

University of Fribourg, Medical and Molecular Microbiology Unit

How bacteria unify to protect against antibiotics

Bacteria that join together to form colonies (known as biofilms) are difficult to break down with antibiotics. We are investigating the ways in which these biofilms are involved in the development of resistance.

Most bacterial infections are caused by biofilms. These are bacterial colonies that form a dense coating to occupy a range of surfaces including those of medical products such as implants. In a biofilm, the bacteria surround themselves with protective gelatinous substances comprised of extra-cellular components. As a result, when treating infections with antibiotics only a small amount of the active agent comes into contact with the bacteria, thus helping to form resistance. In an international research project with partners from four European countries, we are investigating how bacteria in biofilms adapt to antibiotics, how they acquire re-sistance and how this influences the bacterial composition in the biofilm.

Dr. Qun Ren Zulian

Empa, Laboratory for Biointerfaces

Reconciling the profit motive with sustainable use of antibiotics

We aim to develop and test a new incentive model to encourage the development of new antibiotics with particularly robust resistance profiles. Under the model, manufacturers will receive a bonus if an antibiotic retains its effectiveness in the long term and produces little resistance.

The research team is investigating whether a new incentive system could motivate the industry to develop antibiotics and support moderate antibiotic use. The incentive takes the form of a bonus that is awarded at certain intervals if the antibiotic retains its effectiveness and produces little resistance. If the amount paid is large enough, companies will be motivated to encourage careful use of antibiotics. Working with project partners from Canada and Sweden, we are using current drug candidates at an advanced (Phase III) stage of development and a few medicines already on the market to investigate which principles could be universally applied to determine how susceptibility should be measured and how the bonus framework overall could be designed.

Prof. Stephan Harbarth

University of Geneva, Department of Internal Medicine Specialties

Reducing antibiotic use in pig production in Thailand

The rapid increase in demand for meat in Thailand is driving the growth of antimicrobial use on farms. We are developing interventions to improve surveillance against AMR in pig farms considering farmers' practices and attitudes.

In order to develop targeted interventions to reduce the consumption of antibiotics on Thai pig farms, we map emerging resistance and look for links to risk factors. We do so by investigating pig farmers' practices and attitudes, which are compared to samples of antibiotic-resistant bacteria from pigs, farmers and members of their communities who are not in direct contact with the animals. This produces a model in which variables such as antibiotic consumption, animal husbandry and farm structure can be modified, allowing the researchers to test the impact of various measures. Ultimately, our team is examining whether reduced consumption of antibiotics can actually be associated with a lower resistance level in pigs, pig farmers and the community.

Dr. Thomas Van Boeckel

ETH Zurich, Department of Environmental Systems Science

Thomas van Boeckel translates data on antibiotic resistance and pig farming practices into risk assessment maps.

Reduce AMU
IN PIGS

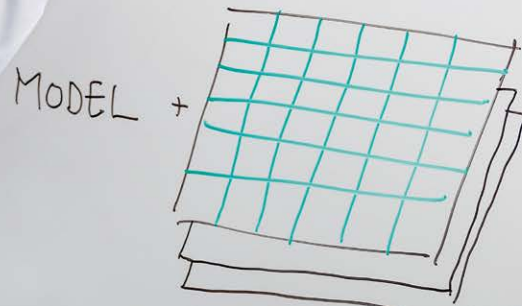
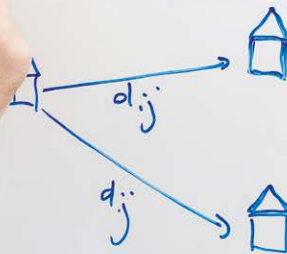
Phase I:

$$R_i = f\left(AMU_i, \text{Con}_i, \sum_{i \neq j}^N \frac{1}{d_{ij}} \cdot AMU_{ij}\right)$$
$$+ R_{ij} = f(e.o.)$$

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RISK M

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Reducing antibiotic resistance in slurry

Slurry and manure are used as organic fertilisers in agriculture. However, they also carry a large number of antibiotic resistances. We are investigating methods to reduce the number and variety of these resistances.

Organic fertilisers are transmitting a large number of antibiotic resistances – both resistant pathogens and individual genetic components that play a role in the development of resistances – to agricultural land. Slurry and manure fertilisers from pig and poultry farms contain a particularly large quantity and diversity of clinically relevant antibiotic resistances. We are performing tests to determine the extent to which composting or anaerobic digestion can reduce resistance. At the same time, we are investigating whether reducing resistance in fertiliser also reduces the number of resistance genes in soil and plants. We will be carrying out these investigations in Switzerland, while other research groups will be testing the same methods in five other countries.

Dr. David Drissner

Agroscope Wädenswil, Institute for Food Sciences

Making healthcare systems resilient to antimicrobial resistance

Considerable efforts are underway worldwide to combat the problem of antimicrobial resistance. We are analysing them in several countries. Our goal is to identify factors that make countries resilient to this challenge.

Not all countries are equally well able to deal with the problem of antimicrobial resistance. The concept of “resilience” is suitable for analysing the necessary factors. Resilience reflects the ability of a system to react to disturbances, and adapt and maintain its vital functions. However, little is known about the fundamentals underlying health systems’ ability to cope with antimicrobial resistance. Our international collaborative project is identifying and measuring the key influencing factors, including animal and ecological factors, in several case studies in different countries.

Dr. Didier Wernli

University of Geneva, Global Studies Institute

AB-Assistant: improving antimicrobial prescribing with a smartphone app

We aim to improve the way antibiotics are prescribed in hospitals by testing a smartphone or tablet app that will help doctors choose the right antibiotic.

We are testing an app that will assist doctors in hospitals when they are prescribing antibiotics. The app contains each hospital's specific recommendations on antibiotic prescribing as well as data on current antibiotic resistance. To assess the impact of the intervention, we will be observing the prescribing habits of a group of doctors who are using the app and comparing it with the habits of another group that is not using it. Since the study is taking place concurrently in various European countries (Switzerland, the Netherlands, Sweden, the Czech Republic) plus Canada, its use can be observed in a number of different contexts.

Dr. Benedikt Huttner

University of Geneva Hospitals, Division of Infectious Diseases

Using and promoting the interface between science and practice

The results of NRP 72 will be implemented in practice.

For this reason, we attach great importance to continuous, open dialogue with a range of stakeholders.

NRP 72 will develop new solution approaches in the fight against anti-microbial resistance. So that our results and knowledge will have the greatest possible effect, we place high value on transferring knowledge and technology into practice. These activities are aimed at diverse stakeholders in different sectors, given the broad range of topics covered by the NRP 72 research projects. Included are new strategies in the practice of human medicine, veterinary medicine and agriculture; new approaches to antimicrobial

drugs and diagnostic methods; and new approaches to preventing the spread of resistance between humans, animals and the environment.

Building and using interfaces

The target groups for practical application are very diverse. They include health-care and pharmaceutical companies, as well as agricultural societies and organisations. We would like to establish an ongoing dialogue with all of them. To do that efficiently, we will organise the knowledge and technology transfer

activities according to the major thematic areas of NRP 72. Within these areas, we will build exchanges between scientists and partners from the practical realm by using existing interfaces but also by creating new possibilities for networking as needed.

Close interaction with StAR

NRP 72 works closely with the government administration, namely with the authorities responsible for implementing the National Strategy on Antibiotic Resistance (StAR). NRP 72 will provide

them with effective and practical recommendations for action. However, the cooperation with StAR will also serve to sensitise researchers to the political processes that are crucial to the success of knowledge transfer. Particularly when it comes to changing behaviour, conflicts of interest between different affected stakeholders, for example, must be taken into account.

Connecting researchers

By bringing researchers from different disciplines together, NRP 72 provides new impetus in the fight against antimicrobial resistance. This interdisciplinary approach offers major opportunities but also poses challenges to communication among scientists. To encourage knowledge transfer between them, NRP 72 provides a range of possibilities, including yearly exchange meetings for all scientists and joint workshops in thematic

areas. The resulting network will strengthen research on antimicrobial resistance beyond the duration of the NRP.

Constant and transparent information

Public communication about the content and organisational processes of NRP 72 supports knowledge and technology transfer. We regularly and openly provide information regarding advances as well as any problems that crop up. This creates credibility and trust, which are essential in giving science a voice in public and political debate.

Procedure





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The Swiss National Science Foundation

The Swiss National Science Foundation (SNSF) is Switzerland's leading provider of scientific research funding. Commissioned by the federal government, it supports research work in all academic fields, from philosophy and nanoscience to biology and medicine. The focus of its activities is the scientific endorsement of projects submitted by researchers. Yearly, approximately 3000 projects are funded by the SNSF with a total amount of approximately CHF 750 million.

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NRP 72 in brief

NRP 72 develops both basic and applied scientific solution approaches to overcoming the problem of antimicrobial resistance. The NRP is funded in the amount of 20 million Swiss francs. The programme's research projects will be conducted in higher education institutions throughout Switzerland and completed in 2021.

NRP 72 has the following objectives

- To discover and disseminate new knowledge about resistance that can disrupt these processes.
- To develop new antimicrobial drugs and faster diagnostic tests to improve medical treatment of humans and animals.
- To develop methods that will help clinicians, veterinarians and farmers to use antibiotics more selectively.