72 NRP

Antimicrobial Resistance
National Research Programme

A one-health approach

Call for proposals

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Content

What are National Research Programmes (NRPs)?

Research carried out by National Research Programmes consists of research projects that contribute to the solution of contemporary problems of national importance. Under the provisions of Article 10, paragraph 2, of the Federal Act on Research and Innovation of 14 December 2012 (version of 1 March 2014) the Federal Council selects the topics and foci to be researched in NRPs and mandates full responsibility for implementing the programmes to the Swiss National Science Foundation.

The Federal Ordinance on the Federal Act on Research and Innovation of 29 November 2013 (version of 1 January 2014, art. 10, par.2 Bst. c. V-FIFG) describes the NRP funding scheme as follows:

"[1] The National Research Programmes (NRPs) of the Swiss National Science Foundation (SNSF) are a means of generating and conducting coordinated research projects that pursue a common goal.

[2] Topics of research are generally appropriate for National Research Programmes if:

a. Swiss research can make a significant contribution to the resolution of the problem;

b. solutions require research contributions from multiple disciplines;

c. research on the problem can be expected to produce research results that have practical applications within a five-year period.

[3] In exceptional cases, an NRP may also be used for the targeted creation of additional research potential in Switzerland.

[4] The following criteria are also taken into consideration in setting forth the topics of National Research Programmes:

a. the programmes can provide the scientific basis for decision-making by the government and administration;

b. the programmes can be conducted with international collaboration."

1. Summary

Since the end of the last century, the world is dramatically facing the increasing spread of antimicrobial resistance. Microorganisms are developing resistance not only to single antibiotic families but also to several of them together (multiresistance). It now happens that clinicians have to manage severe infections by pathogens resistant to all antibacterials available on the market. A number of experts in the field fear that, if no decisive measures are taken, the world might approach a post-antibiotic era. Switzerland as well as the rest of the world, is concerned by this issue due to several factors such as: i) the intensive, often uncontrolled use of antibiotics not only in human or animal therapy, but also in farming and agriculture; ii) the lack of new drug families in the antimicrobial pipeline; iii) the efficient capacity of microorganisms to generate and spread genes encoding resistance; iv) the presence of these genes in microorganisms not only hosted by humans and animals, but also in foodstuff and the environment, including soil and water.

Many international or national organisations, including the World Health Organization (WHO), the World Organisation for Animal Health (OIE) and the European Commission, as well as countries such as the UK, France and the USA support programmes to implement measures that address antimicrobial resistance, hoping to decrease or, at best, to control resistance. Since resistant infectious microorganisms and resistance genes do not respect national borders, the resistance issue has to be addressed by all countries worldwide and, as far as this is possible, by internationally coordinated actions.

Switzerland has been a pioneer in the field of antimicrobial resistance by promoting the multidisciplinary research programme "Antibiotic resistance" (NRP 49) between 2001 and 2006. This programme implemented a monitoring network to detect and analyse antimicrobial resistance (the SEARCH programme, now called ANRESIS). It contributed to our understanding of resistance mechanisms and has provided several tools for the antimicrobial detection. Ten years later, three main reasons justify a new NRP on this topic. First, the dramatic and steady increase of antimicrobial resistance worldwide, including Switzerland. Second, the recent spectacular advances in molecular techniques such as genome sequencing and proteomics, which open new avenues to gain greater knowledge that may lead to innovative tools for the rapid detection of resistance and for the discovery of new antibiotics. Third, the mandate given by the Federal Council to several Swiss federal offices to develop a strategy to deal with this issue (StAR or Strategy Antibiotic Resistance). This strategy calls for research that could be undertaken within the context of NRP 72.

Compared to NRP 49, NRP 72 has a stronger focus on promoting translational research, thus contributing in a practical way both to reducing antimicrobial resistance and decreasing its negative impact on the therapy of infectious diseases. Since antimicrobial resistance genes are present and mobile in human and animal hosts, and the environment, NRP 72 is addressing the issue with a one-health approach. The new programme considers three main aspects: i) increase of knowledge of potential reservoirs of resistance genes and mechanisms of transmission; ii) development of rapid diagnostic techniques and discovery of novel antimicrobial molecules; iii) proposition of human, veterinary and public health recommendations, environmental recommendations as well as intervention measures.

On 24 June 2015, the Federal Council approved the new National Research Programme "Antimicrobial Resistance" (NRP 72) and mandated the Swiss National Science Foundation (SNSF) to conduct the NRP. The overall funding for NFP 72 amounts to CHF 20 million for 5 years of research.

2. Introduction

Background

For thousands of years the fate of humans and animals was heavily linked to bacterial infectious diseases. Only in the last century did this situation improve significantly, thanks to better living conditions, including generalized sanitisation of water and waste, and advances in medicine, particularly the introduction of vaccines and antibiotics. However, the benefits gained by the therapeutical use of the latter have been eroded by the emergence of antibiotic resistance, raising concerns among health authorities particularly since the end of the last century. Since the completion of the previous NRP dedicated to this issue (NRP 49, 2001-2006), antibiotic resistance has been constantly increasing worldwide, prompting WHO, OIE, EC, USA and many other organisations or countries to take action. NRP 49 "Antibiotic Resistance", generated knowledge on the mechanisms of antimicrobial resistance and it supported the development of new detection methods and monitoring systems in human and veterinary medicine. Since then, as mentioned above, the medical challenges have increased dramatically in the area of healthcare-associated infections with an increased trend toward multidrug resistance. Located in its European and international context, Switzerland cannot consider itself safe in a "clean" microbial environment and therefore not under threat. As a result of human mobility and worldwide commerce a multidrug resistant organism that emerged in a given country can spread all over the world, including Switzerland. The same is true with regard to resistance encoding genes which can move from one bacterial species to another by horizontal gene transfer. An example of this is given by the initial recognition around 2008 of the existence in India of the NDM-1 carbapenemase (New Delhi metallo-β-lactamase gene $bla_{\text{NDM-1}}$) and its subsequent spread all over the world, Switzerland included.

In recent years, a number of observations confirmed the existence of reservoirs for resistance genes in wild and farming animals, in the environment (particularly in soil), and the food chain. This offers grounds to launch a new NRP dedicated to this topic, applying broader systemic approaches than those available at the time of NRP 49. Indeed, advances in molecular techniques such as genome wide sequencing and proteomics offer a favourable basis for such studies. There is also a great need to work out and implement in the hospital setting, in veterinary medicine, in the community, as well in agriculture and the food industry, efficient control measures aimed to stop the increasing emergence and diffusion of antimicrobial resistance. The one-health approach is particularly suited to tackling this set of challenges.

The spread of resistant human pathogens is scary

The Annual Epidemiological Report 2013 published on December 2013 by the European Centre for Disease Prevention and Control (ECDC)[1] confirms that the situation is of extreme concern. There are clear indications of a fast and steady spread of resistance, particularly in invasive Gram negatives (*i.e.*, isolated from blood and cerebrospinal fluid) such as extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* (*Escherichia coli* and *Klebsiella pneumoniae*), carbapenemase-producing *Enterobacteriaceae* (*e.g. Klebsiella pneumoniae*), and multidrug-resistant *Pseudomonas aeruginosa*. The situation concerning Gram positives such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Enterococcus faecalis* / *faecium*, is also worrisome, although

[1] European Centre for Disease Prevention and Control. Annual Epidemiological Report 2013. Reporting on 2011 surveillance data and 2012 epidemic intelligence data. Stockholm: ECDC; 2013.

the trend is currently less critical than for Gram negatives. Indeed, MRSA (Methicillin-Resistant *S. aureus*) resistance has stabilised, or is even decreasing in some countries, which shows that the implementation of action plans aimed to control their spread may be effective. This endorses research focussing on the fight and control antimicrobial resistance.

Based on a first ever multi-centre survey in more than a thousand hospitals in 30 European countries, the same ECDC report concludes that 3.2 million patients acquire healthcare-associated infections in Europe each year. Furthermore the report points out the increased percentage of *K. pneumoniae* resistant to third-generation cephalosporins, fluoroquinolones and aminoglycosides, as well to carbapenems, current last-line antibiotics against these bacteria. The European Survey on Carbapenemase-producing *Enterobacteriaceae* (EuSCAPE) gathered information about the spread of carbapenemase-producing *Enterobacteriaceae* (CPE) and carbapenem-resistant *Acinetobacter baumannii* (CRAb) from 38 European countries (i.e. 28 EU Member States, Iceland, Norway, the seven EU enlargement countries and Israel). The report published on November 2013[2] is the base for the above concern and the following conclusions: the rapid and global expansion of CPE and CRAb is a threat to healthcare and patient safety, as it seriously curtails the ability to cure infections. There is an urgent need for a coordinated European effort on early diagnosis, active surveillance as well as guidance on infection prevention and control measures for CPE and CRAb.

The latest report published by the EU ("Summary of the latest data on antibiotic resistance in the European Union", 17.11.2014), unfortunately confirms the above mentioned trend. Furthermore, the first report of the Review on Antimicrobial Resistance commissioned by the UK Prime Minister and supported by the Wellcome Trust states that if no actions are taken to address globally the issue, antimicrobial resistance will cost an estimated 10 million lives every year worldwide by 2050, *i.e.* more than the present annual death toll from cancer[3].

Veterinary medicine, food and nutrition, agricultural and environmental sciences are also concerned

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. Even low concentrations of antimicrobials are believed to favour the emergence and diffusion of resistance genes. Several studies have shown the mobility of resistance genes between the animal, environmental and human reservoirs. Interestingly, CTX-M enzymes, a family of ESBL which has been spreading worldwide in the past few years, very likely originate from the *Kluyvera* species, from which they are mobilised by plasmids, transposable sequences or other mobile elements. *Kluyvera* is a genus widely distributed in nature, occasionally isolated from human and animal clinical samples. After mobilisation from *Kluyvera,* CTX-M enzymes evolve by mutation and recombination to generate the numerous CTX-M clusters presently found among humans. In this context, a number of studies also performed in Switzerland identified plasmid lineages contributing to the dissemination of CTX-M-1 genes in the food chain, the environment and humans.

A number of infective microorganisms are transmissible between animals and humans, either directly or by contaminated foodstuffs. Obviously, the concomitant transmission of resistance to

[2] ECDC, November 2014: Carbapenemase-producing bacteria in Europe. Technical report.
[3] Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. UK Government & Wellcome Trust, 2014.

antimicrobials is also of concern. Of interest is the collection of information in the European Union aimed to follow the occurrence of antimicrobial resistance in zoonotic bacteria isolated from humans, animals and food. A report published in February 2015 jointly by the ECDC and the EFSA (European Food Safety Authority) is focusing on *Salmonella*, *Campylobacter* and MRSA, and their relative resistance patterns[4].

The concept of resistome: a justification for the one-health approach

The resistome includes all the sequences encoding resistance to antimicrobials - expressed or silent – that are present in animal and human pathogens or commensals, as well as in microorganisms present in the environment. All these sequences might be eventually transmissible by mobile genetic elements such as plasmids, transposable elements, phages, etc., and hence contribute to the emergence and diffusion of antimicrobial resistance in clinical isolates. In recent years, a one-health concept has received increasing attention: it recognises linkages among humans, animals and their environments in the context of human health. Since the resistance genes are mobile within all these compartments, it seems obvious that the issue of antimicrobial resistance needs to be addressed holistically by adopting the one-health concept.

National and international research environment

National research environment

Alarming reports on the increase of antibiotic resistance, as exemplified by the spread of ESBLs and carbapenemases, demonstrate more and more society's failure to preserve the precious resources of antimicrobial agents. For example, the significant increase of the percentage of infections by carbapenem-resistant *Klebsiella pneumoniae* right at the Swiss border in Italy over the last three years is unequivocally worrying and presumably will not stop at the country's borders. The threat of entering a post-antibiotic era is within sight because only few antibiotics are currently in development and, should they enter the market, there are no binding commitments regulating their use and protecting them from misuse. Many public and private bodies have recognized the urgent need to address this threat and are ready for joint actions.

As a technologically highly developed society, Switzerland has played a leading role in developing and producing antibiotics, as well in enhancing hygienic measures in hospitals. Early on, Switzerland availed itself of an extensive waste water disposal system. This was followed by efforts to achieve a more targeted use of antibiotics in human medicine and agriculture. Despite positive results, compared to other countries, Switzerland remains in the European midfield with regard to the use of antibiotics and the development of resistances. Political circles have been calling for new measures (e.g. systematic monitoring of antibiotics in humans, animals and the environment; measures in animal husbandry to improve herd health; mandatory ozonation of hospital waste water).

[4] EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control), 2014. EU Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2013. EFSA Journal 2015;13(2):4036, 178 pp., doi:10.2903/j.efsa.2015.4036

In view of the developments in Europe and worldwide, the Swiss Department of Home Affairs and the Department of Economic Affairs, Education and Research have initiated the 'Strategy Antibiotic Resistance Switzerland' (STAR) on 8 July 2013. The Federal Councillors Alain Berset and Johann Schneider-Ammann mandated the Federal Office of Public Health (FOPH), the Federal Food Safety and Veterinary Office (FSVO) (formerly Federal Veterinary Office) and the Federal Office for Agriculture (FOAG) to develop a joint strategy to deal with antibiotic resistance by 2015, *i.e.* the STAR programme. The project will also involve the Federal Office for the Environment (FOEN), the cantons and further concerned parties.

A few years ago, the National Research Programme "Antibiotic Resistance" (NRP 49) contributed significantly to a better monitoring of the antibiotic resistance and allowed initial steps in the management of antimicrobial resistance. Today, NRP 72 will provide crucial research for the implementation of STAR. Due to Switzerland's central location in Europe and the global mobility of people and animals, there is a constant pressure leading to the introduction and diffusion of new multiresistant bacteria in Switzerland. In addition, the use of antibiotics in the country contributes to the emergence of resistance at the national level. In this context, early interventions to control antimicrobials consumption and to detect and then interrupt transmission of resistant bacteria or their genetic resistance determinants is the most hopeful approach to maintain efficacy of antimirobial treatment.

In Switzerland, several highly qualified groups are involved in surveillance and research activities dealing with antimicrobial resistance including basic and applied aspects, at the human, animal, food, and environment levels: this is an essential precondition to reasonably guarantee the success of NRP 72. The institutions hosting research groups that may contribute to this NRP include the Swiss Federal Institutes of Technology (ETHZ, EPFL), cantonal universities and hospitals, the Swiss Federal institute of Aquatic Sciences and Technology (EAWAG), the Federal Research Stations Agroscope, several High Technical Schools. In addition, a number of start-up companies are also involved in the discovery of new antimicrobial molecules. Surveillance and research areas currently developed in Switzerland include:

- Assessment of antibiotics and antimicrobial-resistance genes in the environment, including wastewaters, sewage, manure, surface waters, soil;
- Mechanisms of antibiotic resistance, particularly for aminoglycosides and β-lactams;
- Genetics of antimicrobial genes and resistant bacteria (typing, phylogeny, evolution);
- Antibiotic resistance in animals and veterinary medicine;
- Antibiotic resistance in the food chain;
- Antibiotic resistance in the environment, including soil and water;
- Diagnostics and rapid detection of resistance genes;
- Surveillance and epidemiology of antimicrobial resistance (see in particular www.anresis.ch);
- Report on sales of antibiotics in veterinary medicine and antibiotic resistance monitoring of livestock in Switzerland (ARCH-Vet)[5];
- Antibiotic stewardship plans and implementation and analysis of infection control measures to decrease the burden of antibiotic resistance;

[5] http://www.blv.admin.ch/dokumentation/04506/04518/index.html?lang=en#sprungmarke3_13 or https://www.swissmedic.ch/marktueberwachung/00135/00136/00181/index.html?lang=en

- Discovery and identification of novel antibiotics, including the search of new targets for antimicrobials.

International research environment

The increasing resistance of microorganisms against therapeutic agents has raised concern worldwide and stimulated many countries and organisations to improve surveillance and take action to control the extent of the phenomenon. In April 2014, WHO published the report "Antimicrobial resistance: global report on surveillance 2014"[6]. As accurate as is presently possible, this document provides a first picture of the magnitude of antimicrobial resistance and the current state of surveillance at a global level. In the United States, President Obama signed an Executive Order directing key Federal departments and agencies to take action to combat the rise of antibiotic-resistant bacteria. The Administration also released its "National Strategy on Combating Antibiotic-Resistant Bacteria" [7] . The document outlines five interlinked goals involving "partners in healthcare, public health, veterinary medicine, agriculture, food safety, and academic, Federal, and industrial research". Interestingly (and in line with the scope of NRP 72), among the five goals, the following can be highlighted: i) Strengthen national one-health surveillance efforts to combat resistance; ii) Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria; iii) Accelerate basic and applied research and development for new antibiotics, other therapeutics and vaccines. Similarly, in February 2015, the second report of the Review on Antimicrobial Resistance commissioned by the UK Prime Minister indicated five steps for actions to be taken without delay, which are also in line with the objectives of NRP 72: i) Increase basic science funding to tackle antimicrobial resistance; ii) Make existing drugs go further; iii) Support the development and use of relevant diagnostic technologies; iv) Invest in the people who will solve the problem; v) Modernise the way surveillance of drug resistance is done and used globally[8].

EASAC (European Academies Science Advisory Council) has also been concerned with antimicrobial resistance for the past few years: it produced a number of reports and recommendations, the last one in October 2014 ("Antimicrobial drug discovery: greater steps ahead"[9]).

Moreover, the recent developments in antimicrobial resistance outlined by the competent European Authorities, *i.e.* ECDC (European Centre for Disease Prevention and Control) and EFSA (European Food Safety Authority)[10] indicated that there is urgent need for concerted actions. In the EU, antimicrobial resistance is considered one of the ten 'major societal challenges'. In its Recommendation adopted on 27 October 2011 on the research Joint Programming Initiative 'The Microbial Challenge – an Emerging Threat to Human Health" (Joint Programming Initiative Antimicrobial Resistance JPIAMR, see below), the European Commission (EC) recognises: "The microbial challenge, due to the increasing resistance to antimicrobial drugs, represents one of the major emerging threats to human health in the 21st century. It is estimated that more than 25,000 patients die in the European Union each year from infections caused by bacteria that are resistant to multiple

[6] http://www.who.int/drugresistance/documents/surveillancereport/en/
[7] https://www.onehealthcommission.org/documents/news/AR_Sept_2014_national_strategy_33603346EF092.pdf
[8] Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a global health crisis: initial steps. UK Government & Wellcome Trust, 2015.
[9] http://www.easac.eu/home/reports-and-statements/detail-view/article/antimicrobia.html
[10] http://www.efsa.europa.eu/en/efsajournal/doc/3590.pdf

antibiotics, so-called multidrug-resistant bacteria. Resistance rates to a single antibiotic exceed 40-50 % in some European countries, and resistance to multiple antibiotics is a common and growing problem" [EUR-Lex – 32011H1028(01), 27.10.2011, p. 1.]. The Recommendation estimates that the overall direct costs to society in terms of extra healthcare costs and productivity losses will reach EUR 1.5 billion each year in Europe, with indirect costs "several times higher".

In response to the EC Recommendation mentioned above, a proposal coordinated by Sweden for the Joint Programming Initiative on antimicrobial resistance (JPIAMR) has been submitted on 20 March 2012 and was adopted by the Commission on 08 June 2012. In December 2013 the Management Board (MB) of the JPIAMR approved the Strategic Research Agenda (SRA) which foresees Joint Research Calls over the next few years in the following six Priority Topics: Therapeutics, Diagnostics, Surveillance, Transmission, Environment and Interventions. More precisely, the JPIAMR aims to improve existing antibiotics, develop new ones and devise further therapeutic approaches, e.g. vaccines, together with industry partners. Other objectives include improving diagnostics, setting up an international programme to monitor antibiotic resistance, multi-disciplinary research on how resistance spreads, studying the environmental impact of antibiotics and resistant organisms as well as developing improved prevention and control measures. The SRA was officially launched in Brussels on 3 April 2014. Switzerland is member of the MB.
As a final conclusion, it should be pointed out that to be successful, the actions undertaken to fight antimicrobial resistance should be multidisciplinary (holistic) and internationally coordinated within Europe, hopefully involving also developed and developing countries outside the continent.

Practical significance and target audience

The powerful and substantial implementation of the 'Strategy Antibiotic Resistance Switzerland' (STAR), issued by the Swiss Confederation will, among other factors, greatly depends on the contributions and results of NRP 72. For this reason, the partners and stakeholders of STAR will be greatly interested by the research performed within this NRP. The investigation on the resistome within medical and agrifood settings, as well the whole environment, may lead to new intervention strategies necessary to combat efficiently the resistance problem. Novel rapid diagnostic techniques, innovative therapeutics (including novel types of molecules), anti-virulence and anti-persistence approaches, and alternative treatments in human health and food production systems, will be pursued on the basis of mandatory knowledge on the transmission routes and the bottlenecks that govern the spread of the resistome within and between humans, animals, plants and the environment. Improved knowledge of transmission will be crucial for the implementation of new efficient control measures.

A few projects performed within NRP 72, mainly those related to the search of new bacterial targets for therapy or novel antibacterial molecules, might be of great interest for existing or upcoming start-ups. Indeed, NRP 72 will provide some financial support for proof-of-concept and pre-clinical assays.

Finally, some of the results to be obtained by the programme might well be used to improve academic and professional training in all fields of health care. Indeed, reliable and documented observations always help to realise the importance of control measures – sometimes cumbersome - implemented to control the spread of infectious diseases and antimicrobial resistance.

3. Goals of NRP 72

Scientific goals

The ultimate objective of the programme is to contribute to reducing antimicrobial resistance as well as decreasing its negative impact on the therapy of infectious diseases. This objective will be reached: i) by developing new tools and techniques aimed to track antimicrobial resistance, particularly in the environment and the food chain; ii) by further studying the mechanisms, pathways and vectors involved in the development and diffusion of antimicrobial resistance in humans, animals, the food chain and the environment, particularly identifying the dynamics of the resistance-encoding gene transfer between these reservoirs (one-health approach); iii) by stimulating the research of rapid diagnostic techniques aimed at identifying in human and animal hosts colonisations and infections that do need antibiotic therapies, and at detecting resistant microorganisms or the genes involved; iv) by stimulating the research on "old" and novel antimicrobial compounds (including inhibitors to be used in combination), in particular by supporting the proof-of-concept and pre-clinical assays (*i.e.* in animals) of interesting leads discovered by basic research; v) by developing and testing antibiotics stewardship and infectious diseases control plans aimed to develop strategies to decrease the emergence and diffusion of resistance.

The transdisciplinary networking of leading national and international researchers (in particular with EU groups) is one of the programme's overarching goals. Integration of proposals in the JPIAMR programme is another feature of NRP 72. The system-wide, integral approach is also to be incorporated in teaching activities at higher education institutions. In addition, a consensus platform for science, politics and the economy is to be built as a basis for implementing the national strategy against antimicrobial resistance and to deliver recommendations on how to implement a national reference centre and standard repository.

Goals of knowledge transfer

An important goal of knowledge transfer of NRP 72 is the collaboration with public and health care management groups and extension services. The aim of this collaboration is to develop effective awareness campaigns to sensitize the public and the health care personnel about the resistance issues, and to facilitate the implementation of new measures to limit the spread of antibiotic resistance. In this context, the establishment of a consensus platform may be useful to communicate facts and formulate recommendations.

Another goal of knowledge transfer is the provision of the concerned Federal offices with science-derived data and information useful for the implementation of effective measures to decrease the antibiotic consumption and the antimicrobial resistance diffusion.

Finally, the development of new diagnostic tools and antimicrobial compounds will be of interest to the diagnostic and pharmaceutical industries, particularly if proof-of-concept and preclinical studies have been successfully achieved.

4. Main research topics

In order to fulfil the objectives mentioned above, the research programme should address themes and areas with research projects of high practical relevance. The questions or topics that can be addressed include:

- How and where do specific resistances arise and where are their reservoirs found?
- How are multiresistance emergence and transmission influenced by the therapeutic or preventive use of antibiotics and disinfection measures in human and veterinary medicine?
- How are the transmission pathways of these resistances structured in different, environments (hospitals, animals, water, soil, etc.)?
- Identification of novel diagnostic techniques including reliable point-of-care assays and rapid screening strategies.
- New therapeutic approaches or other intervention studies in the field of infection control based on new insights (novel diagnostic procedures, interventions).
- How can resistance developments and interactions be monitored by interlinked surveillance systems in human, animal and environmental settings (one-health approach)?

More precisely, the projects to be submitted should belong to one of the three modules indicated below.

Module 1: Potential reservoirs and mechanisms of transmission

In this module, mechanisms of transmission and potential reservoirs will be investigated using up-to-date and powerful new techniques that have been developed in the recent years. When possible and feasible, the one-health approach will be applied. The most urgent research topics to be considered are the following:

- Nature of the resistome and its sources, especially for clinically significant multidrug resistant Gram negative bacteria; what are the potential reservoirs, mechanisms of resistance as well as the mechanisms of resistance selection, transmission, spread, and their bottlenecks?
- Dual role of biocides in clinical environments as compounds capable of controlling infections and selecting antimicrobial resistance.
- What are the mechanisms of co-selection, co-amplification and transmission leading to an increased appearance of multiresistance in commensals and pathogens in animals and humans, taking into account therapeutic and preventive use of antibiotics and disinfectants.
- Influence of specific antibiotic therapy given to animals in selecting antibiotic resistance microorganisms significant in human medicine or in selecting genes encoding resistance.
- What are the transmission dynamics of antimicrobial resistance in food and agricultural systems (*e.g.* in different effluents such as slurry or drainage water as well as compost, manure and organic fertilizers or dusty air).
- What are the interactions of resistant bacteria (in particular ESBL and carbapenemase producing microorganisms) originating from the above effluents, with the indigenous microbial communities.

- What are the interactions of resistant bacteria (especially ESBL and carbapenemase producing microorganisms) present in food with the indigenous microbiota of the intestinal tract, taking into account potential antagonists of these pathogens.
- What are most relevant transmission pathways between environment, animals and humans (including travel).
- Characterization of gene exchange communities, clonal complexes and gene mobile elements shared by humans, animals and the environment that can be involved in antibiotic resistance origin and transmission.
- How do antibiotics enter the environment and which material flows transport antibiotics? How can we quantify antibiotics entering the environment through human medicine (via waste water into natural waters) and through veterinary medicine into the soils?
- How should the environmental monitoring of antibiotics and their active agents be designed so that it can gauge the success of measures aimed at reducing antibiotic resistance?

Module 2: Rapid diagnostic techniques, novel antimicrobial molecules

This module will include the search for methods and tools for identifying in clinical samples the presence of resistant pathogens and/or resistance-encoding genes, conceivably providing clinicians useful and reliable rapid diagnostic tests. In addition, the module will include projects aimed at working out novel antimicrobial compounds or identifying bacterial targets essential for the survival of pathogens in living hosts that might be potentially inhibited by natural or synthetic drugs. The topics to be considered are the following:

- Rapid diagnostic tests to confirm the susceptibility to antibacterial drugs of the microorganism(s) involved in an infectious process, and thus drive the potential success of ongoing or alternative therapies.
- Novel diagnostic assays for rapid identification of (multi)drug resistant bacteria.
- Novel diagnostic assays for rapid identification of resistance-encoding genes.
- Development of new tools for preventing the use of broad spectrum antibiotics or for promoting the use of specific-targeted antibiotics.
- Development of "old" drugs for an alternate use to treat (multi)resistant bacteria.
- Development of new molecules to be used as single antibacterial compounds or in combination, *e.g.*, as an inhibitor of a resistance mechanism.
- Identification of novel targets that can be used to develop novel or alternative antibiotics.
- Proof-of-concept and pre-clinical assays for particularly interesting antibacterial compounds (however, large clinical trials of potential antibiotics will not be supported).

Module 3: Implementation measures and public health recommendations

The third module will include intervention studies aimed at developing strategies with the ultimate goal of reducing the antimicrobial consumption and the resistance emergence and diffusion, and hence, of decreasing the risk of therapeutic failures of infectious diseases caused by resistant pathogens. The projects should be of high quality, preferentially randomized or cross-over intervention studies; they should be able to clearly demonstrate the efficacy of the control measures tested. When appropriate, these studies should be accompanied by cost-effectiveness and legal analyses in order to convince the concerned health authorities and the public to implement the proposed measures. This module will include the following topics:

- Development of new tools to drive the implementation of infection control measures.
- Establishment of (multicentre)intervention studies in the field of antibiotic stewardship, both for inpatients and outpatients.
- Establishment of (multicentre)intervention studies in the field of infectious diseases control within hospitals and long term care facilities.
- Implementation of the most relevant established tools for intervention strategies in the field of human and veterinary medicine, as well in the agricultural, food and environmental sectors.
- Development and implementation of animal production strategies that reduce the need for antibiotic use.

5. Characteristics of NRP 72

NRP 72 is a five-year programme and the NRP Steering Committee reserves the right to implement a second, more clearly defined call for proposals at a later date to close gaps left after the first call and to include newly arising research questions. The second call would also allow for new projects, based on the already running research projects in NRP 72, which would lead towards the implementation of research results or a programme synthesis. For projects of a possible 2nd call, a shorter duration will apply depending on the start date of the projects and the end of the research phase of NRP 72.

Whenever appropriate, the proposals submitted to NRP 72 should consider multidisciplinary and multicentre approaches.

Knowledge and technology transfer (KTT) is a particular concern of NRP 72. Whenever appropriate, stakeholder associations (agriculture, food industry, start-up companies, etc.) should be involved early on to work towards collaboration with the Innovation Promotion Agency CTI.

Switzerland is a member of the Management Board of the Joint Programming Initiative "Antimicrobial Resistance" (JPIAMR). The main objectives and core research topics are to a significant extent complementary to those of this NRP 72. NRP 72 researchers may answer calls from the JPIAMR, provided that the thematic of the JPIAMR call fits with the overall goals of NRP 72. Specific funding – a maximum of CHF 3 million is available to support projects with Swiss partners within the European initiatives. Successful participants will adhere to the general rules and guidelines of NRP 72 in particular. Participation in JPIAMR calls and initiatives will be decided by Programmes Division of the Research Council of the SNSF, on the recommendation of the Steering Committee of the programme.

6. Submission procedure and project selection

General conditions

One call for proposals is foreseen. In the event of significant thematic gaps, a second call for proposals may be launched.

Research projects of NRP 72 are limited to a maximum of 48 months. The average budget of a project is expected to range between 300,000 to 400,000 CHF. This range is meant as a reference point. Smaller and larger budgets are possible.

To allow for optimal coordination, approved projects must start no later than three months after the date of the approval.

Cross-border research projects are supported if the competence of researchers from abroad is essential for realising the project. As a rule, the share of financing requested for researchers abroad may not exceed 30% of the overall budget, and the person responsible for the project abroad may not be assigned the role of corresponding with the SNSF. For applicants from abroad, the norms and salary rates of the relevant country will be applied mutatis mutandis, with the SNSF maximum rates generally serving as the upper limit. Before submitting a proposal for a cross-border research project, please contact the programme manager of NRP 72.

A two-stage submission procedure is used for NRP 72: Pre-proposals are submitted first, a selection of proposals is then invited to submit a full proposal. The Steering Committee expects both proposals to be submitted in English.

All forms, rules of procedure and instructions for the submission of proposals can be found on www.mysnf.ch under 'information/documents' after selecting the corresponding NRP and creating an application.

Online submission on mySNF

Pre- and full proposals have to be submitted on the mySNF portal (www.mySNF.ch). For this, user-registration is needed. User accounts obtained in the past are valid and provide access to all the funding instruments of the SNSF. It is recommended to request new user accounts as early as possible, however, they need to be requested no later than five working days before the submission deadline from the homepage of the mySNF portal.

Pre-proposals

The deadline for submission of pre-proposals is 11 January 2016.

In addition to the data that has to be entered directly on mySNF, the following documents need to be uploaded:

- Project description (as PDF file)
  Applicants must use the document template provided on the mySNF portal. The project description must not exceed six pages.
- Short CVs and publication lists of all applicants (as PDF files)
  The CVs must not exceed a maximum of two pages each. Each publication list must contain the five most relevant publications only. Links to full publication lists may be included.

Project descriptions and CVs exceeding the indicated length will not be considered.

Full proposals

The deadline for submission of full proposals is 30 June 2016.

In addition to the data that has to be entered directly in mySNF the following documents need to be uploaded:

- Research plan (as PDF file)
  Applicants must use the document template provided on the mySNF portal. The project description must not exceed 20 pages.
- Short CVs and publication lists of all applicants (as PDF files)
  The CVs must not exceed two pages each. Links to publication lists may be included.
- Supplementary documents (support letters, confirmation of co-operation or co-financing, forms regarding international co-operations, etc.) can be uploaded on mySNF.

Project selection

The Steering Committee evaluates the submitted pre-proposals and makes a final decision based on the review criteria outlined below. In making its decisions, it may refer to international assessments. Authors not invited to submit a full proposal will be informed accordingly by means of a ruling.

In the second stage of the submission procedure, the Steering Committee will invite the authors of the selected pre-proposals to submit a full proposal. In the invitation, the Steering Committee might give recommendations or set conditions for the full proposal. Based on external reviews as well as on their own evaluation, the Steering Committee will propose full proposals to be approved or rejected by the National Research Council (Programmes Division and Presiding Board).

Project teams invited to submit full proposals may be invited to present their projects to the Steering Committee. This presentation colloquium will take place on the following days (please reserve them): 26 and 27 September 2016.

Selection criteria

The Secretariat of the Division Programmes checks whether the personal and formal requirements are met, before forwarding the proposal for content review (cf. Funding Regulations of the SNSF). Pre- and full proposals that do not meet the personal and formal requirements will not be processed further.

Pre- and full proposals will be reviewed on the basis of the following criteria:

- **Compliance with the goals of NRP 72**: proposals must reflect the programme's objectives as outlined in the call and comply with its overall framework.
- **Scientific quality**: proposals must fulfill international state-of-the-art criteria with respect to scientific quality as well as methodology.
- **Scientific originality**: proposals must contain an innovative component and be relevant as compared to completed or running research projects in the same field.
- **Inter- and transdisciplinarity**: projects with research questions addressed by different disciplines or that demand approaches that transcend the boundaries between science and

practice must secure adequate cooperation between the actors, project management and the methodology.

- **Application and implementation**: the potential for practical application and implementation of results is a key element of National Research Programmes. Projects of high practical relevance are therefore given priority.
- **Personnel and infrastructure:** applicants must have a sound scientific track record in the field of the submitted project. Adequate personnel resources and an adequate infrastructure must be secured for the project.
- **Responses to comments given**: the Steering Committee may choose to comment on the pre-proposal and make suggestions for revisions to the research team for the preparation of the full proposal. (This criteria is applicable to full proposals only.)

Schedule

At present, the following schedule is envisaged for NRP 72:

Call for pre-proposals	18 September 2015
Submission of pre-proposals	11 January 2016
Invitation to submit full proposals	March 2016
Submission of full proposals	30 June 2016
Final decision on full proposals	November 2016
Start of research (at the latest)	1 January 2017 (1 March 2017)

Budget

Total funds of CHF 20 million are available for this NRP. The provisional allocation of this funding between the different research modules, administrative activities and participation in JPIAMR calls is as follows:

Module 1: Potential reservoirs and mechanisms of transmission	CHF 4.5 million
Module 2: Rapid diagnostic techniques, novel antimicrobial molecules	CHF 5 million
Module 3. Implementation measures and public health recommendations	CHF 5 million
Participation in JPIAMR calls	CHF 3 million
Knowledge and technology transfer, synthesis, scientific support	CHF 2.5 million

7. Contact persons

For questions regarding the submission of pre-proposals and full proposals, please contact the programme co-ordinator: Barbara Flückiger Schwarzenbach, nfp72@snf.ch or 031 308 22 22.
For questions concerning salaries and eligible costs, please contact the Head of Finances Roman Sollberger, roman.sollberger@snf.ch or 031 308 22 22.

Technical help with *my*SNF and electronic submissions

Hotline:
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E-mail: mysnf.support@snf.ch
*my*SNF Homepage: www.mysnf.ch

8. Actors

Steering Committee

Prof. Christoph Dehio, Biozentrum University of Basel (President)

Prof. Joachim Frey, Institute of Veterinary Bacteriology, Vetsuisse Faculty, University of Berne

Prof. Peter Frey, Institute of Bioengineering, EPFL Lausanne

Prof Petra Gastmeier, Institut für Hygiene und Umweltmedizin, Charité - Universitätsmedizin Berlin, Germany

Prof. Herman Goossens, Laboratories of Clinical and Medical Microbiology, University of Antwerp, Belgium

Prof Susanne Häußler, Dept. of Molecular Bacteriology, Helmholtz Centre for Infection Research, Braunschweig, Germany

Prof Jose L. Martinez, Departamento de Biotecnologia Microbiana, Centro Nacional de Biotecnologia, Madrid, Spain

Prof Jesús Rodríguez Baño, Universidad de Sevilla, Hospital Universitario Virgen Macarena, Spain

Delegate of the Programmes division of the National Research Council

Prof. Dr. Isabelle Mansuy, Brain Research Institute, Laboratory of Neuroepigenetics, University/ETH Zurich

Programme Manager

Dr. Barbara Flückiger Schwarzenbach, SNSF

Head of Knowledge Transfer

N.N.

Representative of the Swiss Federal Administration

Karin Wäfler, Project Leader of the Swiss National Strategy against Antibiotic Resistance (StAR), Swiss Federal Office of Public Health (FOPH), Berne

For the State Secretariat for Education, Research and Innovation (SERI), Berne

Dr. Claudine Dolt, SERI, Berne