72 NRP
Antimicrobial Resistance
National Research Programme

FASTER DIAGNOSTICS AND NEW THERAPEUTIC APPROACHES

Thematic Synthesis of the National Research Programme "Antimicrobial Resistance"

Swiss National Science Foundation

November 2022

Contents

About this thematic synthesis

The National Research Programme “Antimicrobial Resistance” (NRP 72): Developing solutions to the threat of antibiotic resistance

Against the background of increasing antibiotic resistance, the Swiss National Science Foundation launched the National Research Programme "Antimicrobial Resistance" (NRP 72) on behalf of the Federal Council in 2017. In 33 projects at Swiss universities and higher education institutions, as well as 12 international projects within the framework of the European Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), scientists investigated various aspects of the problem.

The aim of NRP 72 is to identify new solutions that contribute to the containment of antibiotic resistance. The programme was therefore planned and implemented in coordination with the Swiss Federal Strategy against Antibiotic Resistance (StAR).

Conclusions and recommendations for three overarching topics

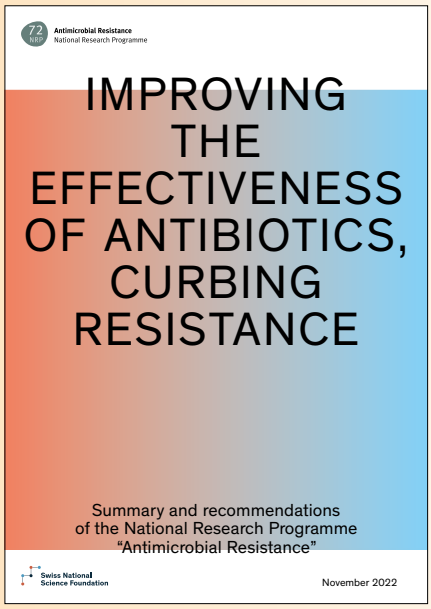
In addition, researchers synthesized their results in on three overarching topics, corresponding to the three research modules of NRP 72:

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

For each topic, a working group of researchers analysed research results from different professional perspectives, put them in a larger context and discussed them with a sounding board representing relevant stakeholders as well as with members of the NRP 72 Steering Committee (see Annex 1 for involved persons). From these processes emerged three thematic syntheses, which elaborate scientific findings of NRP 72 and formulate recommendations for action.

The thematic syntheses stand on their own and reflect the view of the researchers’ working groups. However, together they form the central basis on which the NRP 72 Steering Committee derived its overarching conclusions on the most important fields of action and measures that result from the findings of the programme.

All three thematic syntheses and the overall programme summary can be consulted on www.nrp72.ch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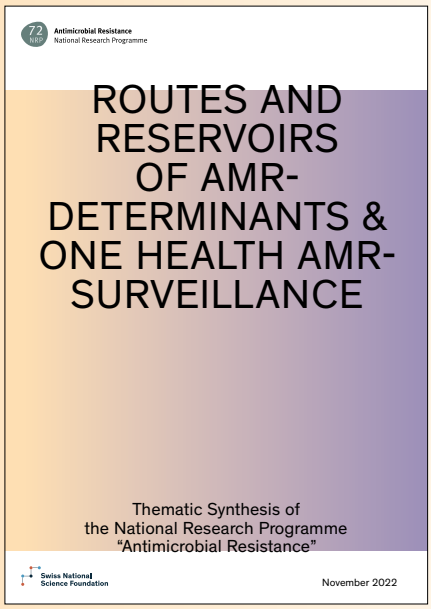
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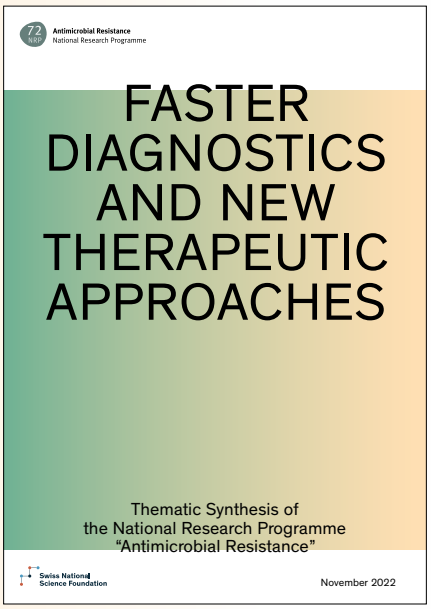
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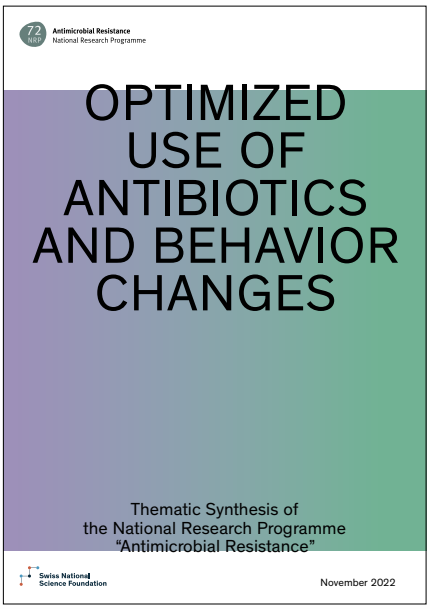
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Executive summary

This thematic synthesis “Faster diagnostics and new therapeutic approaches” was drafted by a working group of researchers from the SNSFs National Research Programme “Antimicrobial Resistance” (NRP 72). The synthesis process was supported by two members of the NRP 72 Steering Committee and a sounding board representing relevant stakeholders. All these persons are listed in the publication details at the end of this report.

The aim of this synthesiss process was to derive recommendations from NRP 72 research that promote the implementation of new findings in practice. A large part of the discussions revolved around the development of new medicines. With good reason: While the NRP 72 projects convincingly and clearly show that antibiotic resistance can be overcome with novel mechanisms of action, and that academic research can systematically deliver promising new approaches to therapies, results are hardly applied today. After the initial development phases it is rare for novel antibiotics to reach the pre-clinical and clinical stages, which is the area of smaller and larger companies. The development costs are too high in light of the expected profits a novel antibiotic generates on the market. Today, the main problem facing antibiotic development is primarily a lack economic attractiveness due to market failure.

Against this background, the working group, together with the sounding board, has discussed the current framework conditions for antibiotic development and analyzed possible solutions that are currently being developed and evaluated by other countries such as Sweden and the United Kingdom. On this basis, five central recommendations for action are presented, which take into account Switzerland’s specific situation:

1. Secure long-term push funding for excellent AMR basic research and education in Switzerland.
2. Increase resources to develop innovative partnerships for the pre-clinical and clinical development of antibiotics in Switzerland.
3. Improve reimbursement schemes for innovative diagnostic tests
4. Implement a Swiss pull incentive through subscription models and fair remuneration for novel antibiotics.
5. Play an active role in the global fight against AMR through partnerships.

If effective antibiotics are to be available to medicine in the long term, it is imperative to act in these areas. Above all, adjusting the market conditions for antibiotics will be unavoidable. This can only happen if the necessary course is set at the highest political level. Many of the recommendations formulated in this report are therefore addressed directly to the federal government, knowing that it must and can initiate these processes.

1

Introduction: New diagnostics and therapies are needed, but unfavourable conditions hinder their development

Chapter summary

The problem is driven by overuse of antibiotics – faster diagnostics would help to optimise this.
Antimicrobial resistance (AMR) is a growing problem of global dimension. Antibiotics belong to the most important discoveries of medicine, and patient safety in hospitals and in particular in intensive care units critically depends on functioning antibiotics. It is well recognized that the extent of the global AMR crisis has its roots in the massive misuse of antibiotics over several decades, both in veterinary and in human medicine. To slow the spread of AMR, industrialized countries have significantly reduced antibiotics usage in both veterinarian and human medicine and pertinent antimicrobial stewardship programmes have been implemented. With the AMR problem exacerbating in Swiss hospitals, rapid and specific diagnostic testing becomes increasingly important. Only with accelerated diagnostic testing, adequate antibiotic treatment can be adjusted rapidly. This allows for swift escalation or de-escalation of antibiotic treatment and thereby contributes to antimicrobial stewardship and patient safety. The implementation of innovative diagnostic methods is associated with additional costs. It is therefore important to recognize the long-term value of better and faster diagnostic testing. Thus, decisions on covering the associated costs should not be guided by short-term considerations.

Antimicrobial stewardship is key, and so are new antibiotics
Current and future stewardship measures that mainly aim to reduce antibiotics consumption will only slow down, but not stop, the spread of AMR. Therefore, it does not suffice to implement more decisive or even radical antimicrobial stewardship programmes to overcome the AMR crisis. Instead, it is imperative to discover and develop novel antibiotics and alternative antimicrobial treatments. Academic research on antibiotics discovery at Swiss universities is performed at a very high international level, and the respective projects funded by NRP 72 have resulted in excellent publications. However, the antibiotics market is unattractive for several economic reasons, resulting in a severe lack of investments in the clinical development of antibiotics. Furthermore, the AMR crisis is not equally severe across the globe; in Switzerland, the number of yearly deaths caused by AMR is estimated to amount to around 270 and thus is currently comparatively low.

The existing push mechanisms to promote antibiotic development must be complemented by adequate pull mechanisms
Since the AMR crisis is not (yet) severely impacting health systems in wealthy countries, the pipeline for novel antibiotics undergoing clinical trials is still dry. The situation is even more pronounced for antibiotics licensed for animals. In recent years, governments across the globe have made major investments in supporting antibiotics research by means of so-called “push incentives”, namely, to boost innovations mainly at research universities. More recently and driven by international initiatives such as CARB-X and the Novo Repair Action fund, substantial push funding was targeted towards translational research and early development SMEs. While these investments are very important and need to be sustained, they do not suffice on their own to fix the problem of the broken antibiotics market. Therefore, concepts to implement so-called “pull incentives” are currently being discussed, but have not yet been implemented at an adequate scale. The basic concept behind pull incentives is to delink profits from sales volume of antibiotics, for example by subscription models, thereby complying with the concept of antimicrobial stewardship. While some European countries such as Sweden or the UK play a pioneering role in running pilot programmes on pull incentives, Switzerland has thus far played a passive role that neither represents Switzerland’s capacity in drug innovation and development nor does it reflect the country’s economic power or its aspiration for leadership in global health security.

The Swiss Government must take a more active role in promoting antibiotic development

Our working group strongly advocates that the Swiss Government take an active role in fighting the AMR crisis by improving the economic framework conditions for the development of novel antibiotics and by significantly increasing its financial engagement in this domain. As a neutral country hosting several international organizations dedicated to fighting AMR, excellent research institutions and a strong life science sector, including numerous SMEs and one large pharma company at the international forefront of clinical development of antibiotics, Switzerland is in a unique position to actively contribute to one of the biggest global challenges of the 21st century.

1.1 Significant gaps in the promotion of antibiotics developments

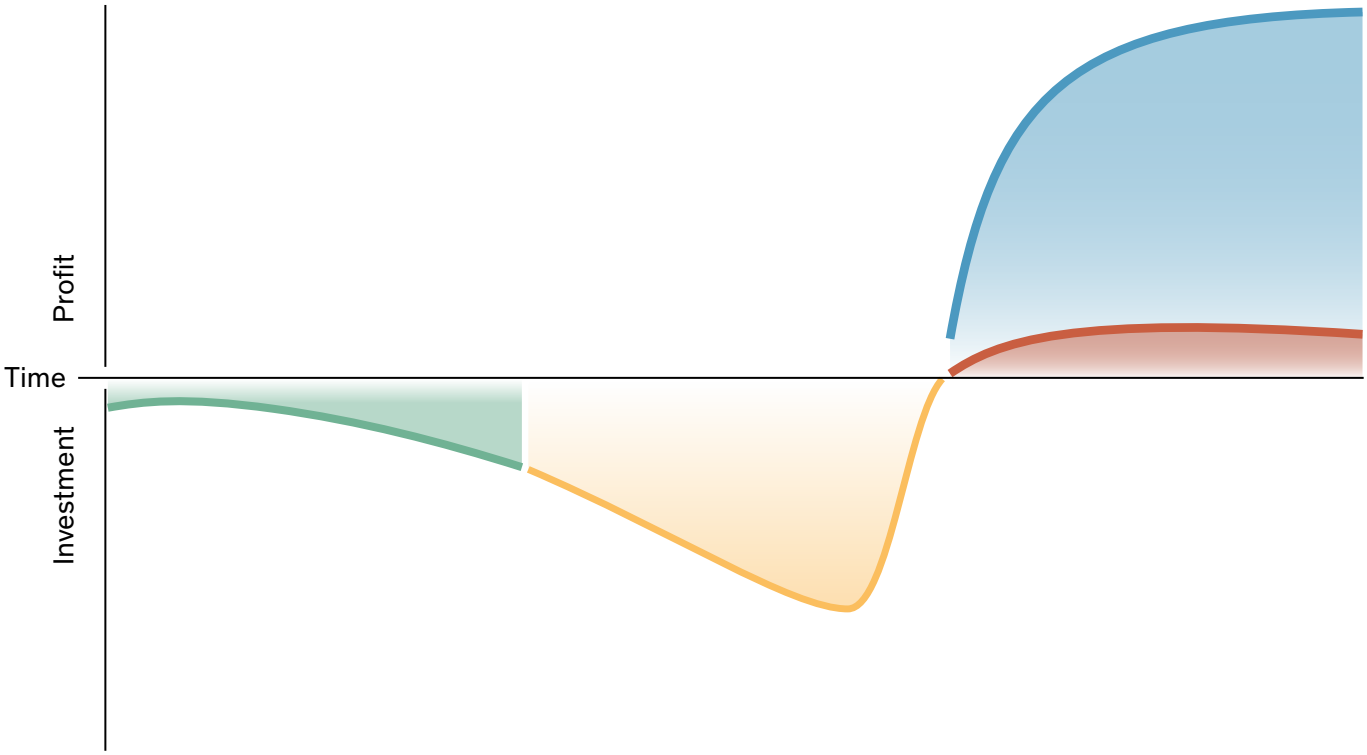
Much is being done about AMR, but significant gaps remain

The AMR problem has been widely recognized as one of the biggest challenges of modern medicine, and several international and governmental organizations have presented corresponding action plans, including the World Health Organization (WHO) launching the global action plan on antimicrobial resistance in 2016 (https://www.who.int/publications/i/item/9789241509763), the European Union (https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance_en) and national authorities around the world (for example the Centers of Disease Control and Prevention in the United States: https://www.cdc.gov/drugresistance/index.html). In Switzerland, the corresponding activities are bundled within the Swiss Strategy on Antibiotic Resistance (StAR; https://www.star.admin.ch/star/en/home.html). The Swiss Centre for Antibiotic Resistance (ANRESIS) provides surveillance data on the prevalence of bacterial resistances and the consumption of antimicrobial drugs (https://www.anresis.ch) in humans, while in the veterinary field the Federal Food Safety and Veterinary Office (FSVO) handles data on antimicrobial resistance and antibiotic use. The National Reference Center for Emerging Antibiotic Resistance (NARA) (https://www.unifr.ch/med/nara/fr) has a mission to detect the emergence of new forms of resistance.

Common to most action plans are strategies to confine the development and spread of AMR by reducing antibiotics consumption and improving diagnostic testing. Furthermore, Switzerland has launched three academic research initiatives (NRP 49, NRP 72 and NCCR AntiResist), which are important and promising programmes, but are not sufficient in size and scope to tackle the AMR problem. More importantly, they are not fully exploited, as additional push funding would support translational science based on the early academic discoveries from the research initiatives moving to SMEs. Investment and a clear strategy on pull mechanisms would close the innovation circle by allowing the private sector to co-invest and remunerate novel antibiotics not by volume, but by availability protecting humankind from future pandemics.

Failing market incentives for antibiotics

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



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

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

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

Expected profit after market approval:
market for antibiotics, as novel drugs are sold in low volumes due to antibiotic stewardship programmes and prices are regulated at low levels

Faster diagnostics and new therapies are priorities, and their development should get more support

On the international scene, the UK had played (and still plays) a prominent role in developing strategies to combat AMR. Activities bundled in "The Review on Antimicrobial Resistance" and commissioned by former UK prime minister David Cameron in 2014 culminated in the widely acclaimed O'Neill report in 2016 (https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf). The O'Neill report concluded that without corrective measures, AMR could claim 10 million lives per year in 2050, and thus lead to estimated costs of US$100 trillion yearly. The report exposed a lack of appreciation for the real (economic and societal) value of antibiotics and suggested ten interventions to effectively fight AMR, which would cost around US$4 billion yearly. This corresponds to 0.05 % healthcare expenditure in the G20 countries. The O'Neill report listed three interventions that are of high relevance for our thematic synthesis: i) Promoting new, rapid diagnostics to cut unnecessary use of antibiotics, ii) Establishing a Global Innovation Fund for early-stage and non-commercial research, iii) Creating better incentives to promote investment in new drugs and improvement of existing ones.

In a nutshell, massive additional investment in the development of innovative diagnostics and novel antibiotics is urgently needed to prevent disastrous consequences.

In the wake of the 2016 O'Neill Report, new initiatives were launched

The O'Neill report was a wake-up call to bring the AMR crisis high on the political agenda of the G20 (https://www.oecd.org/germany/g20-health-ministers-meeting-fighting-antimicrobial-resistance.htm) and the G7 countries (https://www.gov.uk/government/publications/g7-health-ministers-meeting-june-2021-communique/g7-health-ministers-meeting-communique-oxford-4-june-2021). In recent years, several initiatives and funding schemes have been implemented at the international level, with the USA, the UK, Germany and the European Union playing leading roles in this process.

The World Health Organization and Drugs for Neglected Diseases Initiative (DNDi) founded the Global Antibiotic Research and Development Partnership (GARDP) as a not-for-profit organization in 2016 with the aim of developing new antibiotic treatments for drug-resistant infections that pose the greatest threat to health. GARDP, now an independent Swiss Foundation, is based in Geneva and has obtained major financial support from several European Countries, with the largest contribution (€60 million) from the German Government. Switzerland has committed €1.2 million through the Federal Office of Public Health. Until 2021, GARDP has secured €97 million in funding (https://gardp.org/uploads/2021/07/GARDP-financialreport-2020.pdf).

In the USA, the "Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator" (CARB-X) was founded as not-for-profit organization, which funds antibiotics development projects worldwide. Major sponsors of CARB-X are the US government through Biomedical Advanced Research and Development Authority (BARDA) and National Institute of Allergy and Infectious Diseases (NIAID), the Wellcome Trust (a large charitable foundation in the UK), and the German Government. With a total of US$361 million invested between 2016 and 2021, CARB-X is the largest funding body of its kind. Notably, several Swiss SMEs developing novel antibiotics have received major contributions from CARB-X, including Spexis (formerly Polyphor), BioVersys, Basilea Pharmaceutica International, Idorsia and Debiopharm, testifying to the excellent quality of pre-clinical and clinical-stage antibiotics development at Swiss companies.

Most recently, the AMR action fund was initiated with the aim of investing more than US$1 billion by 2030 to bring 2–4 new antibiotics to the market (https://amractionfund.com/). The AMR action fund has secured funding from more than 20 pharmaceutical companies, including the large Swiss pharmaceutical companies Novartis and Roche. The AMR action fund intends to invest in smaller biotech companies with a focus on innovative treatments with novel mechanisms of action. It was initiated by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), which has its main quarters in Geneva.

1.2 New momentum in Europe, Switzerland remains passive

Europe is committed to tackling the AMR problem

In analogy to the SARS-CoV-2 pandemic, which revealed the disastrous consequences of an infectious disease taking an unprepared world hostage, the AMR crisis has recently been dubbed the "silent pandemic" [1]. As a positive consequence of Covid-19, the political will to finally respond adequately to the AMR crisis was strengthened. In the context of the Horizon Europe Work Programme on Health, ideas are being collected on how pull incentives can be implemented in Europe. The experience with the advance purchase agreements for Covid-19 vaccines will be analyzed to this end. The president of the European Commission, Ursula von der Leyen, urged the establishment of a European version of the US counterpart BARDA, called the European Health Emergency Preparedness and Response Authority (HERA), whose main task will be to increase European preparedness for global health threats in general and infectious diseases in particular (https://www.europarl.europa.eu/legislative-train/theme-promoting-our-european-way-of-life/file-european-biomedical-research-and-development-agency). While it remains to be seen how these European activities affect the implementation of adequate pull incentives for antibiotics, it is clear that the Covid-19 crisis has generated considerable momentum to tackle the AMR problem in Europe.

Switzerland remains rather passive internationally

In contrast, the Swiss government has thus far played a rather passive role in the global fight against AMR, in particular in the costly domain of developing novel antibiotics by creating the much-needed pull incentives. On top of that, Switzerland is excluded from essential multi national projects in this field (e.g., HORIZON-HLTH-2021-IND-07-02 on developing a European pull incentive) due to the lack of affiliation with the EU Horizon Programme. In particular, the aforementioned SMEs are now completely excluded from EIC Accelerator grants and sidelined for programmes of the Innovative Medicines Imitative (IMI) and financing programmes of the European Investment Bank (EIB). The lack of leadership and involvement in the field on the part of Switzerland will lead to a loss of global influence in finding an adequate solution to the AMR challenge and could result in a lack of access to innovative antibiotics.

The investments of the federal government to fight AMR sum up to roughly CHF10 million or 0.01% of its healthcare spending (CHF82 billion in 2019 according to the Federal Statistics Office), i.e., CHF20 million for the NRP 72 programme (running from 2017–2022), about CHF60 million for NCCR AntiResist (running from 2020–2031) and €1.2 million for GARDP. This spending is clearly below the target of 0.05% of healthcare expenditure recommended by the O'Neill report.

So far, no success for political initiatives to promote antibiotics development

On a regular basis, the Federal Council (and in some cases also the Swiss parliament) have rejected motions and postulates handed in by Swiss parliamentarians that asked for the implementation of a Swiss pull incentive scheme (https://www.parlament.ch/de/ratsbetrieb/suche-curia-vista/geschaeft?AffairId=20204529 and https://www.parlament.ch/de/ratsbetrieb/suche-curia-vista/geschaeft?AffairId=20194291), increased support of companies active in antibiotics development through additional tax reduction (https://www.parlament.ch/de/ratsbetrieb/suche-curia-vista/geschaeft?AffairId=20193551), the establishment of a Swiss funding scheme to develop novel antibiotics (https://www.parlament.ch/de/ratsbetrieb/suche-curia-vista/geschaeft?AffairId=20193860), or the organization of an international high level governmental meeting aimed at improving the framework conditions for antibiotics research (https://www.parlament.ch/de/ratsbetrieb/suche-curia-vista/geschaeft?AffairId=20194326). Hence, the Swiss government and to some extent the Swiss parliament refuse to fundamentally increase Switzerland's financial contribution to fight the AMR crisis. Rather,

the Federal Council argues that Switzerland's contribution is already sufficient, that the problem has to be tackled at the international level (and thus cannot be tackled within Switzerland alone) and that the AMR problem "cannot only be tackled through the development of novel antibiotics" (response of Federal Council to the Motion 20.4529).

Conclusion: The economic framework conditions for antibiotic development need to be changed

In conclusion, the problem of the spread of AMR has been broadly recognized in Switzerland. However, the Swiss government has thus far focused on reducing the use of antibiotics (which is cost-effective and surely needed), but is reluctant to adequately (co)-finance the development of novel antibiotics, e.g., through the implementation of pull incentives or through other significant financial contributions that reflect the wealth of the country.

Governments of industrialised countries (including Switzerland) urgently need to change the economic framework conditions for the development of novel antibiotics by implementing pull incentive mechanisms, ideally in a coordinated manner on a global scale. To make this happen, the federal and cantonal governments must be ready to substantially increase their current budgets to tackle AMR.

2
NRP 72 research on new diagnostics and therapies

Chapter summary

NRP 72 module 2 focused on three research areas, namely the discovery of novel antibiotics, the development of alternative antimicrobials and the acceleration of diagnostics through novel rapid techniques.

A total of 13 projects were carried out in the context of NRP 72 Module 2. Five projects aimed at the discovery of novel small molecule antibiotics, namely novel aminoglycosides, inhibitors of the novel antibiotic target BamA, chemically engineered antimicrobial peptides and novel antimicrobial compounds deep-mined from host microbiomes. Two projects were aimed at the development of novel antimicrobial treatments either via phage-derived endolysins or entire phages. The remaining six projects were aimed at the development of rapid diagnostics using an array of innovative technologies, including microfluidics, optical fibre technology, nanosensors and small antibodies called nanobodies.

An overview of the major findings of these projects is provided below. In Chapter 3, challenges and opportunities pertaining to the implementation of these NRP 72-related projects are given, followed by recommendations regarding implementation of academic projects towards market products, as well as general recommendations for improving the framework conditions to drive clinical development of antibiotics and the routine implementation of rapid diagnostics.

2.1 Focal points of NRP 72 research: Antibiotics discovery, alternative antimicrobials, novel diagnostics

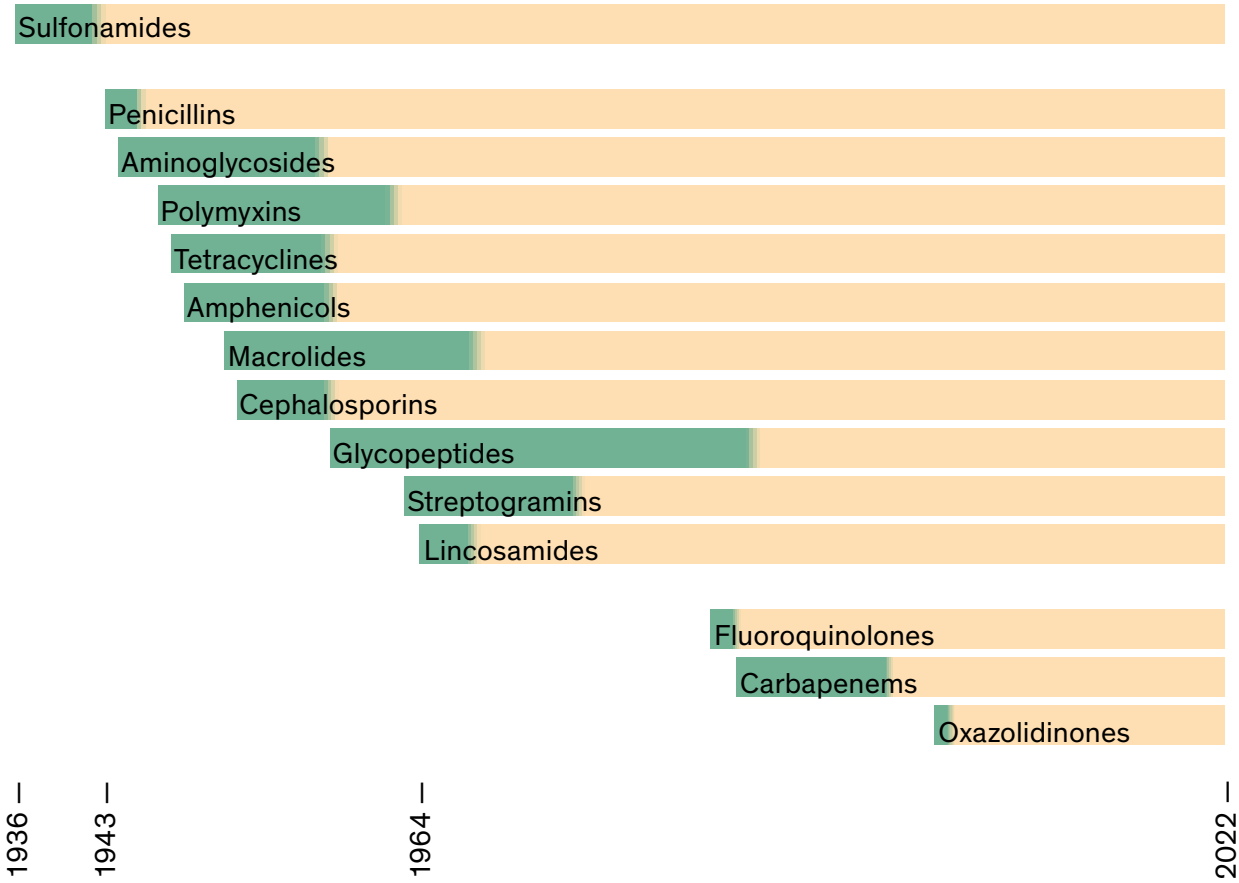
Antibiotics discovery

In a classical sense, antibiotics are small molecule drugs, which are often derived from natural products with antibiotic activity, such as the large class of ß-lactam antibiotics [2]. Most clinical stage antibiotics came to the market between 1940 and 1960, when it was still comparatively easy to identify antibiotic compounds (low-hanging fruits) and when the financial rewards were intact (mainly also due to a lack of restriction on the wasteful and unnecessary use of antibiotics in agriculture, as well as veterinarian and human medicine). Strong competition and low prices subsequently resulted in the retraction of big pharma from the antibiotics market, a subsequent drain of venture capital investments, and a lack of training and education of young talents in the fields of antibiotic development. Although antimicrobial resistance (AMR) had been described as early as the 1940s [3], it is only since the 1990s that AMR has been broadly recognized as a health problem that needs to be tackled at the global level [4]. Currently, the pre-clinical antibiotics pipeline is predominantly in the hands of SMEs mostly located in Europe and North America [5], while in the context of antibiotics currently being assessed by clinical trials [6], companies located in Asia (in particular Japan and China) are also active. It is worth noting that, with the exception of GlaxoSmithKline (GSK), Roche, Pfizer and MSD, large international pharmaceutical companies are not active in the clinical development of antibiotics [6].

With a few exceptions, antibiotics that received market approval in the last ten years are modifications of existing antibiotics with the aim of improving potency, safety, bioavailability, biodistribution, serum half-life, or to overcome resistance mechanisms [6]. By contrast, new compound classes that act through novel mechanisms of action are rarely found in the clinical pipeline [6]. However, it is interesting to note that in the pre-clinical pipeline, innovative novel compound classes are highly prevalent; 72 % of them are directed towards novel targets [5]. Importantly, with the degree of attrition of pre-clinical programmes, continued push investment for antibiotics discovery is still needed to supply the pre-clinical pipeline with the next generation of innovative lead compounds [7, 8].

Market launch of the most important classes of antibiotics

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



Alternative antimicrobials

Alternative antimicrobials include all treatments that do not fall into the class of classical small molecule antibiotics. Alternative antimicrobials are phages, phage-derived proteins, antibodies, vaccines, immuno-modulators, anti-virulence approaches, and microbiomes/microbiome modulators [5]. In clinical practice, alternative antimicrobials still play a minor role. Noteworthy examples of currently approved alternative antimicro*bials* are anti-toxin antibodies administered in the context of *Clostridium botulinum*, *Bacillus anthracis* and Clostridium difficile. However, in the realm of the pre-clinical antibiotics pipeline, roughly 40% of the compounds/treatments fall into the category of alternative antimicrobials, with phage therapies and antibodies being prominently represented [5]. Clinical development of alternative antimicrobials is particularly challenging because current frameworks of clinical trials do not offer the flexibility needed for innovative treatments.

Novel diagnostics

Adequate diagnostic testing is at the heart of antimicrobial stewardship, as it allows for timely de-escalation or escalation of the empiric antibiotic treatment [9]. Especially in the context of life-threatening, acute infections, such as for example blood stream infections, the time within which a diagnostic test provides a result has a strong influence on patient outcomes. Therefore, there is a strong need for rapid diagnostic methods. Acceleration often goes hand-in-hand with miniaturization (e.g., microfluidics), rapid resistance pattern readouts or growth-independent enrichment and/or analysis of pathogens, e.g., through capture technologies and/or deep sequencing in a metagenomics context.

2.2 Research highlights

Highly successful NRP 72 research shows that science provides new solutions

In the context of the research project led by Sebastian Hiller, several high-ranking papers on novel molecules targeting the essential outer membrane protein BamA of *E. coli* were published. These papers describe the discovery of novel OMPTA compounds (chimeric antibiotics contain a ß-hairpin peptide macrocycle linked to the macrocycle found in the polymyxin and colistin family) (Luther et al., 2019, Nature, Ref. [10]), and provide a structural explanation for how the natural compound darobactin binds and thereby inhibits the BamA barrel protein (Kaur et al., 2021, Nature, Ref. [11]). The lab of Jörn Piel developed a novel bioinformatics platform that enables *de novo* structural predictions for trans-AT PKS-derived polyketides from highly aberrant trans-AT PKS biosynthetic gene clusters, thus providing a tool to discover novel antibiotic compounds belonging to the chemical class of polyketides from poorly studies microbes (Helfrich et al., 2019, Nature Chemical Biology, Ref. [12]). Further, the labs of Jörn Piel and Julia Vorholt studied the antibiotic production and biosynthetic potential of the *Arabidopsis* leaf microbiome and via genome mining discovered a large number of previously uncharacterized biosynthetic gene clusters and hundreds of bacterial strains secreting compounds exhibiting antibiotic activity (Helfrich et al., 2018, Nature Microbiology, Ref. [13]). Works in the lab of Jean-Louis Reymond describe nearest-neighbor searches in chemical space to improve the activity of a previously identified antimicrobial peptide dendrimer and thereby identified a novel antimicrobial peptide exhibiting an expanded activity range against Gram-negative pathogenic bacteria and increased serum stability (Siriwardena et al., 2018, Angew Chem Int Ed Engl, Ref [14]).

In summary, these (and further) high-ranking publications emanating from the NRP 72 programme testify to the excellent international standing of Swiss academic research in the domain of AMR research and antibiotics discovery.

A selection of individual research projects is presented in the following chapters 2.2.1 and 2.2.2. The texts correspond to the descriptions of the completed projects on the NRP 72 website, which are aimed at interested laypersons. Further and continuously updated information, including scientific publications, can be found for each project under the respective link to the SNSF Data Portal. An overview of all projects that have researched new diagnostics and therapies within the framework of NRP 72 can be found on page X.

2.2.1 Highlights in antibiotics discovery and alternative antimicrobials

Project: “Ecosystem- and genome-guided antibiotic discovery”

Principal Investigator: Prof. Jörn Piel, Institute of Microbiology, ETH Zurich
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/167051

In nature there are still countless previously unknown substances with antibiotic effects. Many of these are actually produced by bacteria in order to defend themselves against other bacteria. Researchers at ETH Zurich have now developed methods that use the genetic information of bacteria to ascertain directly whether they are capable of producing candidates for substances with effective antibiotic properties. As a result, they have discovered a whole range of promising candidates, in some cases in surprising locations.

Largely unexplored habitats

Many antibiotics used nowadays were developed based on natural substances that produce bacteria themselves to fend off other bacteria. These substances were searched for and found primarily in the soil. But in addition to these, nature offers a huge variety of microbes that represent a major potential source of active substances that remains almost completely untapped. These include, for example, bacteria on plants or in marine organisms. In each of these habitats, the bacteria compete for limited food supplies. This means that they produce a wide variety of substances to prevail over, and defend themselves against, other bacteria.
But not all bacteria are equally active in producing biologically active substances. A team headed by Jörn Piel and Julia Vorholt from ETH Zurich has therefore developed and used bioinformatic methods for ascertaining – directly from the bacterial genetic information – whether an organism might be capable of producing substances with effective antibiotic properties. And, if this is the case, the search tools assess whether these are potential innovative substances or whether they are already known. This is extremely important for antibiotic research, because it searches for new compounds with mechanisms of action that differ significantly from those of existing drugs – and therefore may be able to overcome existing forms of antibiotic resistance.

Several antibiotics with innovative chemical structures discovered

Jörn Piel and Julia Vorholt have initially identified hundreds of bacterial species, including on leaf surfaces, in plant roots and marine sponges. In other studies, they have isolated substances produced by these bacterial species and tested them for their chemical and pharmacological properties. As a result, they have discovered a whole range of antibiotic substances with previously unknown chemical structures. These include a substance, called macrobrevin by the researchers and produced by bacteria, that colonise the leaf surface of thale cress, a wild plant that is widespread in Europe.

For some of the most promising newly discovered substances, the scientists then developed techniques that allow them to be produced synthetically. Naturally produced active substances are often present only in small quantities in environmental bacteria, which poses a major obstacle to further research on drug development, which requires extensive additional tests that go well beyond the initial discovery. Several substances have now been subjected to these tests, and further candidates are likely to follow, since the project has impressively shown that nature can still offer many new antibiotics in widely differing locations. The newly developed methods will prove helpful in the systematic search for these substances.

Project: "The molecular mechanism of outer membrane protein insertion by BamA and its role as a target for novel antibiotics"

Principal Investigator: Prof. Sebastian Hiller, Biozentrum, University of Basel
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/167125

A recently discovered target for antibiotics could help overcome a large number of resistances. Researchers have unravelled the astonishing mechanism behind it, thus paving the way for the development of medicines.

The most dangerous antibiotic-resistant bacteria have one thing in common: they all have a double membrane that is difficult to penetrate. And even if antibiotic agents manage to break through this envelope, the bacteria generally pump them out again straight away. New antibiotics that can kill the pathogens without having to penetrate them could therefore be particularly effective. This is exactly what the synthetic Outer Membrane Protein Targeting Antibiotic (OMPTA) substance class that is currently under development does – as does darobactin, an active ingredient discovered in the natural environment. Both target BamA, a protein on the outer membrane of bacteria. Without BamA, the bacteria are unable to renew their membrane and die.

Bacteria no longer able to form outer membrane

As part of a project conducted under NRP 72, researchers led by Sebastian Hiller at the Biozentrum of the University of Basel were able to elucidate in detail the mechanism of action by which OMPTA and darobactin inhibit BamA. They showed that the two substances imitate a particular three-dimensional structure which otherwise only occurs in the proteins that bacteria produce themselves as the building blocks of their outer membrane. This structure is the key needed to fit the proteins into certain points of the outer envelope from the inside. Both OMPTA and darobactin form a copy of this key, blocking the keyhole from the outside, so to speak. In other words, it is rather like locking the door, then snapping off the key. As a result, the route by which the bacteria transport their envelope building-blocks is sealed off and they die.

Related mechanisms are already known in microbiology and are used by other medicines. The binding structures they target are generally quite large – by microbiological standards, at least. However, the target used by OMPTA and darobactin is very small and impossible to identify using conventional methods. This is despite the fact that the substances themselves are bigger than most active ingredients and would fail to fit through the bacteria's entry gates.

Virtually no resistance

As Hiller and his team have now demonstrated, this target on the outer envelope is the pathogens' Achilles heel. OMPTA and darobactin bind direct to the key "backbone" atoms of BamA. Because these atoms hold

the protein together and determine its form, they cannot readily be modified, despite this being the easiest way for bacteria to develop resistance to these new substances in the foreseeable future. However, darobactin remained effective against all pathogens that Hiller and his team tested in the laboratory and with which resistance can be created artificially. Or, to return to the metaphor: the pathogens were unable to change the lock after it had been picked. Since OMPTA use the same mechanism, pathogens are likely to find it very difficult to develop resistance to this substance too.

These findings are an important step towards potential use in medicine. Using them, it will be possible to specifically improve OMPTA and darobactin and develop them into effective medicines. They could also provide a starting point for other novel active ingredients to combat the most dangerous antibiotic-resistant bacteria.

Project: “Aminoglycoside Drug Development”

Principal Investigator: Prof. Erik Christian Böttger, Institute of Medical Microbiology, University of Zurich
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/166998

Thanks to new insights into how the molecular structure of antibiotics is linked to their mechanism of action, researchers have been able to identify new, highly promising aminoglycoside antibiotics.

Aminoglycoside antibiotics are effective against a large number of bacterial pathogens, including Enterobacteriaceae, Staphylococci and tuberculosis bacteria. They are often the treatment of first choice for severe, life-threatening infections in the hospital setting, despite their sometimes considerable side effects. In recent decades, however, bacteria have become increasingly resistant to these antibiotics.

This is why researchers led by Erik Böttger at the University of Zurich want to develop new aminoglycoside antibiotics. Their aim is to modify the chemical structure of certain aminoglycosides in such a way as to equip them to overcome existing resistances while at the same time improving their side effects profile. Such specific modifications have only recently become possible thanks to knowledge gained about the complex connections between the molecular structure of aminoglycosides and their mechanism of action, including those relating to undesirable effects.

Effective against resistant pathogens

As part of an NRP 72 project, the researchers focused on molecular residues that earlier work had identified as starting points for addressing important aminoglycoside resistance mechanisms in bacteria. In the course of their work, Böttger and his team analysed the precise molecular make-up of such a structure and the role it plays in efficacy against *Pseudomonas aeruginosa* bacteria. Chronic and recurrent *Pseudomonas aeruginosa* infections are a major problem for patients with cystic fibrosis in particular. In the course of their research, Böttger and his team were able to identify an aminoglycoside derivative that exhibits activity against antibiotic-resistant *Pseudomonas aeruginosa* in laboratory experiments. It also produces substantially fewer side effects in animal models.

Hope of treatment with fewer side effects

These results raise hopes that a treatment for chronic *Pseudomonas aeruginosa* infections that causes fewer restrictive side effects is within reach, for example for patients with cystic fibrosis. The in-depth results are

also delivering additional important information on the relationship between aminoglycoside structure and the medicines' effects. As such they provide an important knowledge resource and an innovative framework for the development of aminoglycoside antibiotics going forward.

Project: "Partnership against Biofilm-associated Expression, Acquisition and Transmission of AMR (BEAT-AMR)"

Principal Investigator: Dr. Qun Ren Zulian, Eidg. Materialprüfungs- und Forschungsanstalt EMPA
Dr. Matthias Buhmann, Eidg. Materialprüfungs- und Forschungsanstalt EMPA
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/166998

Bacteria that join together to form biofilms are difficult to treat with antibiotics. Often only part of the used active substances can reach their target, which promotes the development of resistance. Researchers at EMPA have systematically investigated how this happens for the first time in an international project. Their insights can facilitate the development of targeted treatment strategies.

Biofilms protect bacteria against antibiotics

Most bacterial infections are caused by biofilms. These are bacterial cells together with their self-produced matrix 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 extracellular components. As a result, when treating infections with antibiotics only a fraction of the active agent is able to come into contact with the bacteria, leading to sub-lethal concentrations of antibiotics and thus helping to generate resistance. In the international research project BEAT-AMR, with partners from Switzerland, Germany, the UK and the Netherlands, Qun Ren and colleagues at EMPA investigated how bacteria in biofilms adapt to antibiotics, how they acquire resistance and spread them, and how this influences the bacterial composition in the biofilm. There has been no previous systematic research conducted on the influence of biofilms on the formation of resistance.

The team at Empa focused on the identification and characterisation of genes involved in biofilm-specific resistance of *Pseudomonas aeruginosa* towards antibiotics. *P. aeruginosa* is a pathogen of high clinical relevance, responsible for many deadly infections for humans and showing high recalcitrance to current antibiotic treatments. Within biofilms, *P. aeruginosa* cells can resist higher antibiotic concentration than that allowed in the human body. Thus, new therapeutic approaches are urgently needed to improve *P. aeruginosa* removal in the context of biofilm-related infections.

Several genes involved in antibiotic tolerance identified

Qun Ren and her team first established and validated a model system to identify genes involved in biofilm growth and antibiotic resistance. They characterised the important bacterial strain *P. aeruginosa* MPAO1 in much detail, at the genomic level (= totality of genetic information of an organism), proteomic level (= totality of all proteins in an organism), and phenotypic level (= observable physical properties of an organism). They discovered several key genetic determinants responsible for making *P. aeruginosa* biofilms tolerant. Tolerant bacteria are not antibiotic-resistant, but they can temporarily fall into a sleep-like state and thus escape the effect of antibiotics. In this way they persist in patients, often leading to chronic infections that are difficult to treat. Furthermore, tolerance is thought to be a precursor to resistance.

The identification of several sets of genes involved in biofilm-related *P. aeruginosa* tolerance provided important novel insights, which can help to predict the evolution of tolerance in patients and facilitate the development of targeted treatment strategies. Furthermore, a number of genes showed high clinical potential as targets for new antibiotics.

Project: “Antimicrobial peptide dendrimers (AMPD) and bicyclic peptides (AMBP) as therapeutic agents against multidrug resistant bacteria”

Principal Investigator: Prof. Jean-Louis Reymond, Department of Chemistry and Biochemistry, University of Bern
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/167048

Researchers at the University of Bern are creating artificial substances that are similar to known antibiotics. Through targeted modifications, however, they could overcome existing antibiotic resistances and at the same time trigger fewer side effects.

When nothing else works, maybe colistin or polymyxin will. Nowadays these antimicrobial peptides of natural origin are used as last resorts against many multiresistant germs. Yet they can have considerable side effects, and there are now bacteria that are resistant to them. Researchers led by Jean-Louis Reymond from the University of Bern are therefore looking for alternatives that overcome existing resistances while causing fewer side effects. Other peptides offer particular promise in this regard. However, Reymond and his team do not search for them in nature. They develop them with the help of what is known as the chemical space approach. This term refers to the total number of existing molecules that can be used as medicines. Nowadays the chemical space can be explored efficiently using bioinformatic methods and automated chemical synthesis. The reseachers from the University of Bern expanded it to include new molecules that are not found in nature, and which have therefore not been studied previously.

One promising active ingredient turned into many

In this way, they have created several peptides that have proven effective against various bacterial pathogens in initial tests. Among these, they focused on a particularly promising substance called G3KL. Their goal was to further develop this peptide by specifically modifying its molecular structure so that it would have ideal properties for medical use. To this end, they first clarified exactly how the effect of G3KL comes about. Imaging and resistance studies showed that it kills bacteria by a membrane disruptive mechanism, and that bacteria can acquire resistance by changes in membrane composition that are in part comparable yet different from resistance mechanisms against polymyxin. At the same time, these studies led to the surprising identification of several more highly active peptides providing a promising new series of lead compounds.

Now the substances are optimised

The researchers are now optimising them, again by investigating their mechanism of action and assessing which ones might be useful for medical purposes. Furthermore, the project has shown that the methods employed can be used to systematically create new antibiotics that overcome existing resistances. One particular advantage of this approach is that it generates substances that are easy to synthesise and can therefore be optimised. Whether applicable drugs can be developed on the basis of the peptides that have now been generated must first be clarified in further tests.

Project: “Novel targeted bacteriophage endolysin-based approach for treatment of drug-resistant Staphylococcus aureus infections”

Principal Investigator: Prof. Martin Loessner, Institute of Food, Nutrition and Health, ETH Zurich
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/167048

Bacterial viruses destroy bacteria with the help of specific enzymes. Researchers have now succeeded in delivering them in a targeted way to sources of infection deep in the body, and using them there against bacterial pathogens.

Bacteriophages are viruses that kill bacteria but are harmless to humans. They use the bacteria as hosts for the purpose of multiplication. To leave a bacterium, they break down its cell wall using enzymes known as endolysins, causing the bacteria to die. Researchers at ETH Zurich led by Martin Loessner investigated whether and how endolysins can be used to combat local bacterial infections in the human body.

Focus on hard-to-reach infections

While to date, endolysins have already proven successful for external applications, for example on the skin and mucosa, they do not penetrate well into deeper tissue layers. Martin Loessner and his team have now looked at ways to also deliver them to local sources of infection within the human body. Their focus here was on bone inflammations, which are often difficult to treat with the antibiotics available. To fully exploit the therapeutic potential of endolysins, Loessner and his team first analysed a large collection of various endolysins to determine their various properties. Using a screening process specially designed for this purpose, they selected several candidates that function particularly well in the conditions found in the human body and kill specific bacterial pathogens.

Effective in the right place thanks to biological postcodes

To transport these endolysins to precisely the right location within the body, the researchers combined the enzymes with peptide molecules, which can bind to very specific sites such as bone tissue. These molecules reach the desired location virtually automatically when they are circulating in the bloodstream. In this way, they guide the attached active substances – the endolysins – directly to the right place. The researchers therefore also refer to “biological postcodes”. In trials in mice, it was possible to transport endolysins directly to the inflamed bones and kill the bacterial pathogens located in the bone tissue.

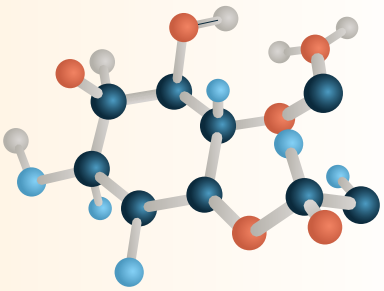
The work by Martin Loessner and his team is an important step towards effective use of endolysins as therapeutic alternatives for treating bacterial infections. They could prove very effective, particularly against bacteria hiding in hard-to-reach areas in the body. In addition, it is extremely difficult for bacteria to develop resistance to endolysins because they perforate the bacterial cell walls in vital places that are difficult to change. Given the increasing issue of resistance, the approach of using the weapons of bacteriophages as medicines harbours significant potential.

Systematically searching for and generating new antibiotics

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

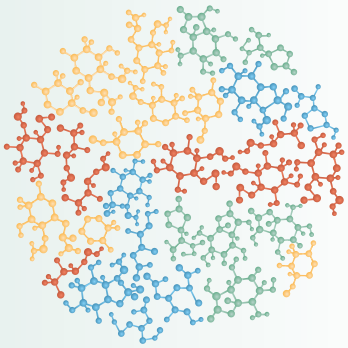
Improving existing and newly discovered active substances

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



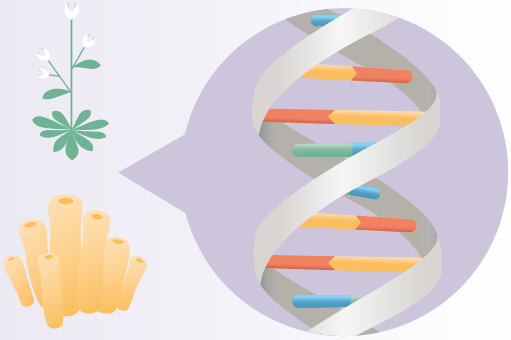
New (artificial) molecules in chemical space

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



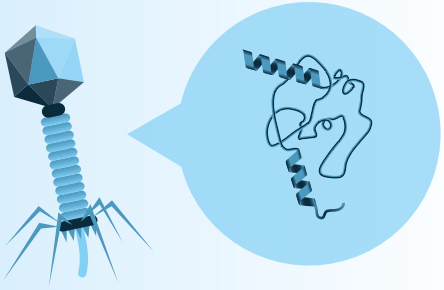
“Genome mining” in nature

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



Bacteriophages

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



2.2.2 Highlights in novel diagnostics

Project: “Rapid diagnostic tests for detection of antibiotic resistance in clinically-significant Gram-negative bacteria”

Principal Investigator: Prof. Patrice Nordmann, Molecular Microbiology Unit, University of Fribourgh
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/177382

Researchers have developed new rapid diagnostic tests that detect antibiotic resistant pathogens.

Early diagnosis of antibiotic resistance is key for the use of antibiotics in order to reduce mortality and limit the emergence of antibiotic resistance. At present, microbiological diagnostic tests are generally used in daily clinical practice because they are able to recognize many resistance genes in pathogens. Patrice Nordmann and researchers from the University of Fribourg have now developed several new antibiotic resistance tests. The researchers focused specifically on difficult-to-treat multi-resistant bacteria of great clinical significance in human medicine, particularly hospital-acquired pathogens such as *Enterobacteraciae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. In addition, some tests may also be used in veterinary medicine.

Choice of methods depends on the pathogen

One of the researchers’ main goals was to shorten the time needed to detect resistance. With many frequently used tests, 24 hours or more pass between the time a sample is taken from a patient and receipt of the result. Patrice Nordmann and his team were able to reduce this time to between 30 minutes and three hours for several of their new tests. To this end, they specifically adapted the test method for different bacteria.

Thus, some of the newly developed tests use biochemical methods that can detect individual substances produced by certain antibiotic-resistant bacteria directly in blood, urine or other samples. One test, for example, identifies the substance nitrocefin, which is produced by bacteria that are resistant to the antibiotic amoxicillin and narrow-spectrum ß-lactam antibiotics, in urine samples. The test can therefore be used in point-of-care diagnostics for urinary tract infections. The researchers are currently still enhancing its sensitivity (= reliability that the pathogen a test is looking for will be detected if it is present) before it is made market-ready. Other tests developed in the project, which detect antibiotic-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (polymyxin resistance) and certain *Enterobacterales* (Rapid ESBL NP, detection of extended-spectrum ß-lactamases), have already received market approval.

Market approval for several tests

The researchers have also succeeded in bringing to market several tests that use either biochemistry or culture-based methods. Here, bacteria are first isolated from samples and placed in a nutrient medium where they multiply rapidly. If a sufficient number are present, either the bacteria themselves or their metabolites can be analysed to obtain information about resistances. Conventional tests using this method usually take a relatively long time, but recently it has become possible to significantly accelerate the multiplication of many bacterial species using specifically adapted nutrients.

The team was less successful with tests using immunological methods. These are based on artificial antibodies and antigens that bind exclusively to very specific sites of a pathogen. If this pathogen is present in a blood, urine or other sample, a corresponding reaction can be observed. However, the antibodies tested

by the researchers were not specific enough, i.e., the tests too often showed a positive result even if the antibiotic-resistant bacterium sought was not present in a sample.

Overall, with several new diagnostic tests already available for clinical use, the project has been enormously successful. Patrice Nordmann and his team are thus making a major contribution to improved treatments and more targeted use of antibiotics. Their tests will contribute to antimicrobial stewardship, which plays a key role in controlling antibiotic resistance, and to the rapid screening of carriers of multidrug resistant bacteria in order to limit their spread in healthcare settings.

Project: “Microfluidic device for ultrarapid phenotypic susceptibility testing of pathogenic microbes”

Principal Investigator: Prof. Petra Dittrich, Laboratorium für Organische Chemie ETH Zürich
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/167123

Researchers at ETH Zurich have developed a miniaturised diagnostic procedure for antibiotic resistance. As it gives reliable results with minute quantities of bacteria, there is generally no need to replicate pathogens. This could greatly speed up diagnosis, enabling more targeted treatments.

No need to replicate pathogens

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. The most time-consuming element of current diagnostic procedures is replicating pathogens from the samples taken. New approaches therefore aim for accurate results with far fewer bacteria. Petra Dittrich's team at ETH Zurich has now developed a method in an NRP 72 project in which minute quantities of bacteria are fixed and analysed on a microchip. This omits the need for the replication step, so that results are available after just 2.5 hours.

The microchip has hundreds of tiny compartments filled with nanoparticle oxygen sensors and antibiotics. Bacteria in fluid are transferred to the chip's compartments using a pipette. The compartments are then sealed with an airtight transparent film. Bacteria sensitive to the antibiotic used subsequently die while any that are resistant survive. Survival can be determined microscopically from the oxygen consumption of the bacteria. In trials using different bacterial species, the differences between sensitive and resistant bacteria were apparent after approximately 1.5 hours; the researchers obtained reliable results after approximately 2.5 hours. These times varied depending on bacterial species.

Observing real processes

Petra Dittrich and her team also developed a variant of their microchips which enables the fluid and bacteria to be filled into the compartments first and an antibiotic to be added at a later point. This is useful for research purposes as it allows scientists to study what actually happens when medication is taken. Among other things, it enables simulation of variations in concentration and microscopic monitoring of their effect on bacterial proliferation. This can provide important information on the development of resistance.
The researchers have demonstrated in their project that microchip-based methods would be suitable in principle for rapid diagnosis of antibiotic resistance. As all instruments required are small, this approach is

highly promising for point-of-care diagnostics, for example in doctors' practices, particularly in areas with less well developed infrastructure where there are no large diagnostic laboratories. Petra Dittrich and her team are now developing the technology further within the National Centre of Competence in Research NCCR AntiResist.

Project: “Microfluidic device for ultrarapid phenotypic susceptibility testing of pathogenic microbes”

Principal Investigator: Prof. Ernst Meyer, Department of Physics, University of Basel
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/177354

The quick and accurate identification of antibiotic-resistant pathogens is often the key to successful treatment. Researchers at the University of Basel have now developed a method that greatly accelerates this diagnosis, while also providing extremely reliable results.

In any treatment of infections with multi-resistant bacteria, accurate identification of the pathogens and resistance types is vital. Traditional methods that are currently used routinely for this diagnosis require relatively large quantities of bacteria, which are multiplied from samples taken from patients. Depending on the pathogen, it can take up to 72 hours before a sufficient quantity of bacteria is available for the diagnosis. Because of this, valuable time that could have been used for treatment is lost. And doctors often resort to using antibiotics haphazardly before clear results are obtained. But this practice promotes the development of resistance.

Sensors bind resistance genes

Ernst Meyer and his team at the University of Basel have now developed a much faster technique employing a completely new technology in this field that uses microscopically small sensors (nanomechanical cantilevers) coated with various biomarkers. These markers precisely match the shape to which individual and very specific genetic sequences of a bacterium bind. As a result, they can be made to specifically bind those sequences that are responsible for various types of resistance. When a bacterial sample containing the relevant sequence comes into contact with a nanosensor, the surface tension of the sensor is measurably changed. This change shows whether a pathogen possesses a specific resistance.

Fast and reliable results

The great advantage of this method is that the bacteria do not need to be multiplied in order to obtain reliable results. Rather, the RNA samples isolated directly from bacteria are sufficient. The researchers in Ernst Meyer's team have now developed sensors that bind various frequently occurring vancomycin resistance genes. In a comprehensive series of tests, their method detected these resistances just as reliably as the existing standard tests, but with a processing time from sample collection to the result of under an hour. This significantly accelerates the diagnostic process.

Comprehensive resistance tests possible

However, the developed prototype is not yet ready for use in practice, since it can be operated only with considerable technical expertise. But given the impressive accuracy and speed of the method, as well as the

comparatively cheap materials involved, it will now be further developed to make it easier to operate. Meyer and his team are also expanding its use to other types of resistance. With several serially connected sensors, comprehensive resistance tests can be carried out very quickly. The next step for the researchers is to focus on diagnosis in cases involving sepsis, since the rapid detection of antibiotic resistance is particularly important in such situations and can mean the difference between life and death.

Project: “A new rapid and reliable bacterial phenotypic diagnostic technique detecting bacterial susceptibility to antibiotics using optical fibers”

Principal Investigator: Dr. Sandor Kasas, Laboratory of Biological Electron Microscopy, EPF Lausanne
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/177354

Researchers developed a new method to identify bacterial resistance very fast. They translated it into a diagnostic device that is easy to use in everyday laboratory work.

An efficient way to limit resistant bacteria proliferation consists in starting the therapeutic process with the most efficient drug against a given infectious agent. For this, fast diagnostics that reveal the resistance profile of a pathogen are needed. But most conventional diagnostic methods used to determine the resistance of bacteria to antibiotics are slow. They take at least one to two days to produce results. Yet patients with serious bacterial infections need to start treatment immediately. In such cases doctors often administer broad-spectrum antibiotics, which can promote the development of resistance but can also lead to treatment failure.

Identifying resistance with glass fibres

A possible solution to this problem has now been put forward by researchers from EPFL. A team led by Giovanni Dietler and Sandor Kasas has developed a method that is considerably faster than previous procedures. It 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.

For the detection of the movements, the team initially used Atomic Force Microscopes (AFM). But these devices are expensive, difficult to operate by non-specialized personnel and not adapted to be used as diagnostic tools. Another drawback is their limitation to operate in parallel. To overcome these hurdles, the researchers developed a novel type of sensors that can be easily parallelized and therefore further increase the response speed by measuring dozens of sensors simultaneously. They tested their new technology in a real-world setting at the Lausanne University Hospital CHUV and compared its results with traditional yet slower methods. It showed that their method is very reliable. Furthermore, the researchers could adapt the technology to the needs of day-to-day clinical practice and improve the handling of the equipment.

Towards broad application in clinical laboratories

Kasas and Dietler founded the start-up company Resistell together with microbiologist Danuta Cichoka. The company has further developed the AFM technology and now offers a diagnostic device that is efficient and easier to use in everyday laboratory work. At present, the devices are mainly used in research. However,

the company is working on a broad market launch for clinical diagnostics in hospitals and medical practices. Furthermore, Resistell will in the future implement the newly developed technology, so it could make a significant contribution to optimising the use of antibiotics in human medicine.

Project: “Rapid diagnostics of blood stream infections using synthetic nanobodies”

Principal Investigator: Prof. Markus Seeger, Institute of Medical Microbiology, University of Zurich
Project on SNSF Data Portal: https://data.snf.ch/grants/grant/177368

Nanobodies are small fragments of antibodies that bind selectively to specific bacterial pathogens. These pathogens can therefore be detected much faster than before directly in blood samples.

It can take several days to detect the bacterial pathogen responsible for blood poisoning (sepsis). A lot of time is lost in current tests because the bacteria obtained from a sample first need to be multiplied for a result. This makes timely, targeted treatment with an appropriate antibiotic difficult. As ever more pathogens are resistant to antibiotics, it is increasingly difficult to choose the right treatment without an accurate test. Faster diagnostic methods could make a vital contribution to lowering the high mortality rate for sepsis.

Better binding sites than traditional antibodies

One approach for faster processes is the use of antibodies to show the presence of specific bacterial pathogens directly in a blood sample or capture them from a blood sample. However, traditional antibodies are not suitable for this, as they generally recognise highly variable sugar chains on the surface of the bacteria, which differ between various strains of the same bacterial species. A team headed by Markus Seeger has now taken a new approach. Instead of variable sugar chains, the researchers targeted conserved protein structures, which barely differ within the same bacterial species. The binding sites of these protein structures are inaccessible for whole antibodies, but can be readily located with much smaller antibody fragments known as nanobodies. Seeger and his team therefore developed different nanobodies to detect and capture the clinically important pathogen *Escherichia coli*, one of the most frequent causes of sepsis. The researchers obtain the nanobodies with the help of alpacas: They inject the animals with components of bacterial pathogens so that their immune systems form antibodies. Parts of these antibodies are then used as nanobodies.

Suitable for diagnostics and food safety

In laboratory testing, clinical *E. coli* strains are successfully captured and detected using nanobodies. Seeger and his team are now generating further nanobodies to be able to detect a broader spectrum of pathogens. They are also working on simplifying the necessary procedures and processes so that this approach can be used as a tool in routine diagnostics. Applications outside of medical diagnostics, such as monitoring foods or drinking water, are also possible. The approach developed could perhaps be used to significantly speed up continuous measurement of *E. coli* bacteria in drinking water, which is common in most industrialised countries nowadays. In collaboration with a company, the nanobodies are being used as reagents to rapidly and reliably detect *E. coli* with a measuring device.

3

Conclusions and general recommendations

Chapter summary

The main goal of most projects of Module 2 was to make some initial steps towards novel antibiotics or innovative rapid diagnostic tests. Hence, it was not within the aim and scope of these projects to generate recommendations that can be directly implemented in practice or that provide data to change policies. Rather, the long-term goal of these projects is to find novel drugs and innovate novel rapid diagnostic methods that may find their way to the market.

In the following sections, we illuminate the impact of the NRP 72 projects in light of their implementation in practice. Furthermore, we pinpoint hurdles in the transition of academic projects into potential market products.

In the second part, we summarize key points addressed by members of the Sounding Board during discussions. Thereby, we address challenges in the pre-clinical and clinical development of antibiotics as well as medical, regulatory, and foremost economic problems associated with the antibiotics sector as part of the pharmaceutical industry.

3.1 Focal points of NRP 72 research: Antibiotics discovery, alternative antimicrobials, novel diagnostics

Challenges pertaining to antibiotics discovery projects

A hallmark of the antibiotics discovery projects conducted within NRP 72 is their diversity. The two projects aiming at the development of novel aminoglycosides ("Aminoglycoside Drug Development" and "Development of novel ribosome-targeting antibiotics") were most advanced and mature in terms of implementation. Since aminoglycosides are a well-known class of antibiotics, the pre-clinical and clinical development path for these new-generation aminoglycosides, as well as their manufacturing process, is comparatively well-defined and foreseeable. On the other side of the spectrum is the antibiotics discovery project "Ecosystem- and genome-guided antibiotic discovery". Highly complex natural products were extracted from their natural source organism, which cannot be produced in larger quantities at the moment. Hence, to further characterize and optimize these compounds with medicinal chemistry approaches, large investments into their chemical or biological production are needed. In contrast, the antimicrobial peptides discovered in the project "Antimicrobial peptide dendrimers (AMPD) and bicyclic peptides (AMBP) as therapeutic agents against multidrug resistant bacteria" can be efficiently produced through chemical synthesis. However, there are clinical challenges associated with antimicrobial peptides, namely biodegradation and general toxicity, which need to be addressed to advance these products further in the pre-clinical and clinical pipeline. Clinical trials performed with the peptide-mimetic murepavadin (Polyphor, since end 2021 Spexis), which recently failed for the systemic (but not the inhalation) route of administration, shine a spotlight on the potential problems encountered in the clinical development of antimicrobial peptides [15]. In terms of novel scientific insights, the project on BamA ("The molecular mechanism of outer membrane protein insertion by BamA and its role as a target for novel antibiotics") was especially exciting, as it revealed the mode of action of a novel natural compound – darobactin – targeting this novel antimicrobial target located in the outer membrane of Gram-negative bacteria [11]. In collaboration with Polyphor (since end 2021 Spexis), the same team characterized novel BamA-specific peptidomimetic compounds (called OMPTAs) [10]. These BamA-targeting OMPTAs show great promise to treat multiresistant Gram-negative ESKAPE pathogens of high priority. As will be outlined in more detail below, all these projects face major challenges from the medical as well as the economic angle.

What becomes evident from looking at the progress made within the NRP 72 projects is the scale of financing needed over prolonged periods of time to build up and maintain expertise in the antibiotics field and to mature antibiotics projects to a point where they are ready for pre-clinical investigation (hit-to-lead). It is

plausible to assume that the full costs to discover and investigate a truly novel antibiotic to the stage where it enters pre-clinical validation (i.e. lead discovery and lead optimization) lies in the range of €1–5 million (depending on the complexity and innovation level of the project)[16]. As such, funding provided by the NRP 72 (around CHF0.35 million per project) only covered a fraction of the costs needed to identify a lead compound. Hence, all antibiotics projects of NRP 72 had a pre-history (funding via other sources) and most of them will need additional funding to reach the maturity level required to enter pre-clinical trials. It is worth noting that the following projects also received highly competitive funding in addition to the NRP 72: Jean-Louis Reymond: "Antimicrobial peptide dendrimers (AMPD) and bicyclic peptides (AMBP) as therapeutic agents against multidrug resistant bacteria": ERC advanced grant; Jörn Piel and Julia Vorholt: "Ecosystem- and genome-guided antibiotic discovery": ERC advanced grant; Sebastian Hiller: "The molecular mechanism of outer membrane protein insertion by BamA and its role as a target for novel antibiotics"), and Markus Seeger: "Rapid diagnostics of blood stream infections using synthetic nanobodies": Joint SNSF Bridge Discovery grant. This testifies to the high level of excellence of the research groups funded by the NRP 72.

Challenges pertaining to alternative antimicrobials

The main aim of the project "Novel targeted bacteriophage endolysin-based approach for treatment of drug-resistant Staphylococcus aureus infections" was to modulate the biodistribution of the phage enzyme endolysin, which is highly active against *Staphylococcus aureus*, including drug-resistant strains, using a homing peptide technology. As planned, homing peptides that direct endolysins into the cell interior have been identified as part of this project. As a future challenge, further clinical applications of the homing peptide technology need to show safety of the product upon systemic administrations; endolysins have so far been used for topical use, mainly in skincare products labelled as medicinal products.

The main goal of the project "Antibiofilm therapy using Local Application of Bacteriophages" was to develop an antibiofilm therapy using local application of bacteriophage. The project entailed the evolution of phage mixtures that would efficiently lyse *Pseudomonas aeruginosa* or *Staphylococcus aureus* often attached to implants within biofilms, and thus very difficult to treat with antibiotics. For future use, it will also be a challenge to manufacture the phage mixture in a controlled manner. Due to the high complexity of the antimicrobial agent (i.e. a phage mixture), the authorization process will likely pose significant challenges.

Challenges pertaining to alternative antimicrobials

In contrast to novel antibiotics, the hurdles to bring novel diagnostic products to the market are significantly lower. Nevertheless, as the workshop "Diagnostics in Antimicrobial Resistance: Pathways from Basic Science to Diagnostic Laboratories" held in 2019 as part of the NRP 72 programme conference revealed, there are several potential roadblocks present in the context of the implementation of novel diagnostic methods. Most importantly, a novel diagnostic method needs to provide a true clinical value that makes a difference at the level of the treating medical doctor in the hospital. Therefore, simply being faster or providing more information is not sufficient on its own for a successful novel diagnostic test. Another important aspect is robustness; in a diagnostic routine lab, the novel test needs to be easy to use and should not require extensive training of employees. And finally, the gain of more information and/or faster time-to-results need to justify the price of a novel diagnostic test. Despite these obstacles, there is a clear trend towards faster diagnostic results, in particular in the context of life-threatening situations such as sepsis caused by bloodstream infections. Furthermore, faster and more precise diagnostic tests are essential to implement and strengthen antimicrobial stewardship programmes, as well as improve patient outcomes and allow therapies that are pathogen-specific (targeted-therapy). The rapid diagnostics projects supported by NRP 72 involved very diverse novel technologies, which hold promise to innovate and significantly accelerate diagnostic tests. Technical innovations are found at the level

of physical engineering, namely rapid resistance testing using microfluidics ("Microfluidic device for ultrarapid phenotypic susceptibility testing of pathogenic microbes"), optical fibers ("A new rapid and reliable bacterial phenotypic diagnostic technique detecting bacterial susceptibility to antibiotics using optical fibers") and nanomechanical arrays ("Fast Assessment of antibiotic resistance in bacteria by using nanomechanical arrays"), as well as at the level of bioengineering of nanobodies ("Rapid diagnostics of bloodstream infections using synthetic nanobodies") and the implementation of established biochemical and microbiological methods into rapid resistance tests ("Rapid diagnostic tests for detection of antibiotic resistance in clinically-significant Gram-negative bacteria").

In terms of implementation, technically complex systems such as microfluidics/microchambers and nanomechanical arrays turned out to be still in a pioneering phase at the end of the project, so the companies approached by the research group leaders were not interested in entering licensing agreements. The devices used in the project are still in a developmental stage and it operating them requires technical sophistication and high expertise, which poses a major hurdle for their implementation in a routine laboratory. A notable exception is the optical fibre technology, which is brought to the market by the startup Resistell (https://resistell.com). Resistell was founded in 2018. Of further mention is an Innosuisse project of Resistell in collaboration with Gilbert Greub (CHUV), which co-finances clinical trials at CHUV. This is a good example of how Swiss funding instruments work hand in hand to advance a highly promising rapid diagnostic method.

It is also worth noting that, the nanobodies identified in the project "Rapid diagnostics of blood stream infections using synthetic nanobodies" are currently being tested by the startup company rqmicro (https://www.rqmicro.com/de_CH/), which were official project partners at the onset of the NRP 72 project. Sequences of nanobodies, which emanated from this project, will be protected by a patent.

In terms of implementation in the diagnostic routine, the project "Rapid diagnostic tests for detection of antibiotic resistance in clinically-significant Gram-negative bacteria" was highly successful and gave rise to three marketed rapid tests to detect polymyxin resistance in *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, as well as ESBL activity in *Enterobacteriaceae* (National Reference Center for Emerging Antibiotic Resistance, NARA, P. Nordmann). Further rapid tests detecting carbapenemase activity, ampicillin, fosfomycin, carbapenem resistance to novel antibiotics in *Enterobacteriaceae* and *P. aeruginosa* are far advanced and are expected to reach the market (NARA). Patrice Nordmann leads this reference centre, which routinely identifies multidrug resistance for hospitals and clinics (and thus is highly aware of the clinical needs). He has established strong ties with industry partners producing and selling diagnostic products, e.g., bioMerieux Inc., Liofilchem Ltd, Chromagar Ltd and ELITech Inc.

3.2 General recommendations based on discussions with the sounding board

In discussions involving the sounding board, we identified several points of high relevance for antibiotics development and novel diagnostics in Switzerland and worldwide. In the light of the global challenge of AMR, these points mainly address issues regarding economic incentives that need to be implemented to fix the broken antibiotics market and how they relate to specific challenges faced by Swiss SMEs and startups that are active in the development of novel antibiotics.

The empty antibiotics pipeline is primarily caused by a lack of economic incentives

The lack of appetite from investors and big pharmaceutical companies for the antibiotics sector is broadly regarded as the key problem underlying the fragile pipeline of novel (pre-)clinical-stage antibiotics. As a

consequence, companies which are active in this field face issues in raising capital, and the entire sector is regarded as economically unattractive. It is considered most efficient to implement pull incentives to render the AMR sector more attractive, with the aim of making private sector willing to invest again. This will secure long-term funding for start-up/SME innovation and secure a link to larger pharmaceutical companies so that more antibiotics will reach the market.

Antimicrobial stewardship programmes can potentially lead to shelving of novel antibiotics

In addition to the broken market, antimicrobial stewardship programmes are seen as a potential cause of the economic failure of novel antibiotics, in particular if the measures result in the shelving of novel antibiotics. On the other hand, it is broadly accepted that novel and last-resort antibiotics are of critical importance for human health. In order to keep them highly effective, novel antibiotics should therefore be used only when appropriate and indicated by the type and resistance profile of the infection. At the same time, it is ethically improper to deny access to novel antibiotics to patients in need, in particular in LMICs. A precondition to ensure appropriate use of novel antibiotics are solid diagnostic test infrastructures.

As for the lack of economic incentives, pull incentives, especially subscription models that delink antibiotics sales from availability, are seen as the appropriate corrective measure. They meet the requirements for antimicrobial stewardship while ensuring access to new classes of antibiotics to safely and effectively treat multidrug-resistant pathogens. The concept of fully or partially volume-delinked reimbursement models has been widely supported by independent research reports (DRIVE-AB, Review on Antimicrobial Resistance (UK), Round Table Antibiotics) and the industry (BEAM Alliance, Biotechnology Innovation Organization (BIO), European Federation of Pharmaceutical Industries and Associations (EFPIA) and International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)).

Value and valuation of novel antibiotics

Sounding board experts advocate for a fair compensation of the innovator via a credible pull mechanism. Mainly for historic reasons, prices of antibiotics are low and often do not reflect the true value they provide to society and the health infrastructure. Therefore, in addition to the broadly discussed and widely accepted pull mechanisms, which completely delink revenues from sales, generating revenues from highly priced novel antibiotics shall remain a valuable option for companies, which plan to commercialize novel antibiotics in Switzerland. The experts advocate for a strengthening of the respective Swiss organizations (i.e., Swissmedic and the FOPH) in the domain of AMR, so that they can jointly facilitate access of innovative antibiotics to the Swiss market at a price that adequately compensates the innovator. An attractive valuation model would send a strong signal to the international antibiotics R&D community. The valuation model should be accompanied by programmes that address the “access question”, namely geared towards providing global access to innovative antibiotics at an affordable price for those patients who need them most, in particular in LMICs.

The attractiveness of the Swiss AMR sector needs to be strengthened as a whole

Sounding board experts representing the Swiss Biotech sector recommend that Switzerland takes an unequivocal stand to support innovators in antibiotic research by optimizing the framework conditions for investors, entrepreneurs, and employees who work in this field. This shall be achieved by targeted tax reductions on potential profits and equity values.

Challenges related to clinical trials and medical authorities

Industrial antibiotic developers consider easy access to clinical trial networks and flexibility in terms of innovative biomarkers and study designs from the side of the regulators as key factors for the number and quality of future antibiotics. Clinical trial networks that allow for efficient and high-quality trials in high-burden countries would be of tremendous help. Collaborative efforts in this regard facilitated by GARDP should therefore be strengthened.

The clinical study designs requested by the FDA, and to some extent the EMA, are considered as outdated and a barrier to bringing more innovative antibiotics and antimicrobial treatments to the market. A related hurdle is that payers expect proof that novel antibiotics are superior to existing ones, but non-inferiority is often the most ethical and/or technically feasible clinical development path. Investigational clinical trials, as often conducted in the (lucrative) oncology sector, would be very important to identify better biomarkers and to innovate better antimicrobial treatments. However, lack of resources to carry out such investigational trials with antibiotics is a major inhibitor of progress towards better biomarkers and more effective drugs.

AMR is a global problem

The experts are well aware that the AMR problem can only be solved at the global level, similar to the global collaboration required to address the Covid-19 pandemic and climate change. Therefore international initiatives such as GARDP, FIND and CARB-X are seen as critical cornerstones in the global fight against AMR. High-income countries need to significantly increase their financial investment in combatting AMR, although the AMR situation in most high-income countries is still tolerable. The experts consider it very important to substantially increase financial support for internationally oriented organizations in a targeted manner, i.e., to focus on organizations that have their headquarters or offices in Switzerland. Given the extensive funding that Swiss SMEs have received from CARB-X over the past decade, it is important that the federal government supports CARB-X financially in the near future and invites the organization to open an office in Switzerland. Likewise, the Swiss government is urged to increase its funding to GARDP and FIND to support these organizations in the global fight against AMR and in establishing collaborative networks, in particular in the context of clinical trials.

Political and public awareness of the AMR problem is still insufficient

Despite major national and international initiatives, public awareness of the AMR problem is still insufficient. Therefore, AMR campaigns need to be continued. Only when the public is clearly aware of the problem can countries justify budget increases to combat AMR.

Switzerland is urged to play an active role in the fight against AMR by establishing innovative pull incentives

Although Switzerland has recently made substantial investments in basic research programmes related to AMR (push funding through NRP 72 and NCCR AntiResist), the experts consider Switzerland's financial commitment to combating AMR to be insufficient. What is basically missing is a national strategy to improve the framework conditions for the pre-clinical and clinical development of antibiotics and antimicrobials. Switzerland, as one of the wealthiest countries, should take responsibility and initiate pull incentives on a national level, following the example of the UK and Sweden. In the longer term, these pull incentives should be harmonized with the EU's pull incentive programmes.

Switzerland is in an excellent position to initiate and support global initiatives that provide access to innovative antibiotics and diagnostics to those who need them most

Switzerland hosts several highly-reputed international organizations, including WHO, GARDP, and FIND, which play a very important role in the fight against the global spread of AMR. The Swiss government is urged to strengthen cooperation and increase targeted financial support for these Swiss-based organizations so that they can provide global access to the latest diagnostic technologies and novel antibiotics needed to detect and treat AMR. An organizational framework, such as that recently established for the COVAX initiative in the context of Covid-19, could provide a basis for such a global AMR initiative. In turn, these organizations, and GARDP in particular, should collaborate with Swiss SMEs to facilitate efficient and high-quality clinical trials in high-burden LMIC countries.

4

Specific recommendations for action

Recommendation 1

Secure long-term push funding for excellent AMR basic research and education in Switzerland

Target audience: Swiss universities, funders, the Swiss government, cantonal governments, philanthropic initiatives, the pharmaceutical industry.
Initial situation/need for action: Research excellence and education in the domain of AMR is crucial for scientific innovations and thus have a strong impact on future research and development of new antibiotics in Switzerland. With the current SNSF NCCR AntiResist, major push funding in the domain of antibiotics development is secured. However, NCCR AntiResist will come to an end in 2031. To ensure long-term stability of funding, Swiss universities, and funders from the private sector are urged to provide the resources needed to maintain the current level of excellence in basic research and education.
Benefits of suggested change: Improved antimicrobial stewardship, diagnostic stewardship and patient information (owner information in veterinary hospitals) will reduce the risk of resistance transmission during a hospital stay and after discharge of the patients from hospitals.
Implementation: Swiss universities and major Swiss funding agencies (SNSF and Innosuisse) are highly recommended to work out long-term plans to maintain and strengthen research excellence in AMR, in particular antibiotics discovery, identification of emerging antibiotic resistance and development of rapid diagnostic methods. The establishment of public-private partnerships for the founding of a dedicated Swiss research institute for AMR is encouraged.
Benefits of suggested change: Long-term funding will secure high-level basic research in antibiotics and rapid diagnostics research and provides a stable basis to educate and train tomorrow's experts in the AMR field.

Recommendation 2

Increase funding for the development of innovative partnerships for the pre-clinical and clinical development of antibiotics in Switzerland

Target audience: Swiss government, funding agencies
Initial situation/need for action: The Swiss-based SME biotech industry has demonstrated strong competitiveness at international level and has received major contributions from international organizations (foremost CARB-X) and from European funding schemes (Horizon 2020 programme) for their pre-clinical and clinical development of novel antibiotics. However, Switzerland has lost its association with the EU Horizon programme and it is questionable whether the US-based organization CARB-X will support the Swiss-based SMEs to the same extent in the future, given the complete lack of financial support from Switzerland towards CARB-X.

With GARDP and FIND, Switzerland hosts two renowned international organizations with an excellent track record in initiating and maintaining partnerships and networks with LMICs in the field of clinical development of antibiotics and antimicrobial stewardship. However, financial support towards GARDP and FIND from the federal government is modest. Finally, basic research conducted at Swiss universities frequently results in research findings that have high translational potential, as is the case for many projects of NRP 72. However, this innovation potential is only insufficiently translated into potential products.
Implementation: The Swiss federal government is strongly encouraged to financially support CARB-X to an

extent that matches the contributions of CARB-X to Swiss-based SMEs, and invite this renowned international organization to open offices in Switzerland. The Swiss federal government is urged to substantially increase its financial contributions to GARDP and FIND in order to strengthen the international activities and collaborations of these Geneva-based organizations and their AMR research and education programmes. Swiss funding agencies, Innosuisse in particular, are encouraged to implement funding schemes supporting academic "bench-to-bedside" projects for novel antibiotics and diagnostic tests.
Benefits of suggested change: The international position of Switzerland as an innovation hub for antibiotics development is strengthened.

Recommendation 3

Improve reimbursement schemes for innovative diagnostic tests

Target audience: Federal Office of Public Health (FOPH), health insurance associations
Initial situation/need for action: Cost considerations are a major implementation hurdle for novel innovative diagnostic tests. It often takes the FOPH years to add a new diagnostic tool to the list of services reimbursed by health insurers.
Implementation: The FOPH is recommended to improve its mechanisms in the context of diagnostic tests and their reimbursement, in order to remove potential hurdles to innovative diagnostic testing. The reimbursement schemes should incentivize medical doctors, diagnostic laboratories, and hospitals to adequately use and constantly improve diagnostic testing, and thereby to strengthen surveillance and antimicrobial stewardship programmes.
Benefits of suggested change: Better framework conditions and attractive reimbursement models for novel diagnostic tests will improve patient outcomes, which in turn has the potential to reduce treatment costs and support antimicrobial stewardship programmes.

Recommendation 4

Implement a Swiss pull incentive through subscription models and fair remuneration for novel antibiotics

Target audience: Swiss government, Swiss parliamentarians
Initial situation/need for action: Pull incentives have been broadly recognized as the most effective element to fix the broken antibiotics market. Implementation of international pull incentives will be a long process, likely taking another 5–10 years. So far, Switzerland has played a passive role in this process. Switzerland has its independent regulatory agency (Swissmedic) and an independent authority to set pricing (FOPH), and therefore has the capacity to commit to fair remuneration models for novel antibiotics.
Implementation: The Federal Council, together with the Swiss Parliament, is urged to commit to a fair remuneration process for novel antibiotics. It is highly recommended to implement an economically credible national pull incentive mechanism for novel antibiotics, which is aligned with antimicrobial stewardship programmes. In addition to subscription models akin to the ones implemented recently in Sweden and the UK, remuneration via competitive pricing as well as other pull incentives should be evaluated. To achieve these goals, it is recommended that the Swiss government strengthen AMR expertise within Swissmedic and

the FOPH. The framework conditions for the commercial AMR sector should be improved by tax reductions for investors and entrepreneurs of this sector.

Benefits of suggested change: A national pull incentive mechanism sends a strong signal to the international community and offers the opportunity to test and validate different pull incentives. A clear and unequivocal commitment to supporting innovators in antibiotics research by optimizing the framework conditions for investors, entrepreneurs and employees strengthens the attractiveness of the Swiss AMR sector.

Recommendation 5

Play an active role in the global fight against AMR through partnerships

Target audience: Swiss government, Swiss parliamentarians

Initial situation/need for action: AMR is a problem of global scale. It is therefore important to tackle the AMR problem at the international level and to ensure access to (novel) antibiotics for those who need them most. With GARDP, FIND, and WHO, Switzerland hosts several international organizations that are at the forefront of the global fight against AMR. Furthermore, Switzerland maintains excellent relations with nearly all countries in the world and is ideally positioned to play an active role in coordinating international AMR initiatives. However, Switzerland is not currently making a contribution to the global fight against AMR that is in line with its political possibilities and its economic strength.

Implementation: The Federal Council, together with the Swiss Parliament, is advised to increase its financial contribution to the global fight against AMR. Therefore, it is highly recommended to increase financial contributions towards established international not-for-profit organizations having their headquarters in Switzerland (namely GARDP, FIND) and towards organizations that play a vital role in financing the pre-clinical development of novel antibiotics at Swiss-based SMEs (namely CARB-X). The Swiss government is encouraged to coordinate global initiatives together with GARDP and the WHO to provide patients in LMICs with access to (novel) antibiotics. Switzerland should also reinforce its research partnerships with European countries and European organizations.

Benefits of suggested change: Increased long-term funding of international AMR initiatives such as GARDP, FIND, and CARB-X will strengthen Switzerland's position as a reliable partner and is in line with the Swiss humanitarian tradition. By coordinating international discussions on the manufacturing, distribution and financing of (novel) antibiotics, Switzerland contributes to fair access to antibiotics worldwide.

Overview on NRP 72 and JPIAMR projects on new diagnostics and therapies

Aminoglycoside Drug Development
https://data.snf.ch/grants/grant/166998
Project lead: Erik Christian Böttger | University of Zurich

Development of novel ribosome-targeting antibiotics
https://www.jpiamr.eu/projects/ribotarget/
Project lead: Erik Christian Böttger | University of Zurich

ESBL-MS: Early diagnosis of ESBL Enteriobacteriaceae in patient samples
https://data.snf.ch/grants/grant/177449
Project lead: Dirk Bumann | University of Basel

Microfluidic device for ultrarapid phenotypic susceptibility testing of pathogenic microbes
https://data.snf.ch/grants/grant/167123
Project lead: Petra Dittrich | ETH Zurich

The molecular mechanism of outer membrane protein insertion by BamA and its role as a target for novel antibiotics
https://data.snf.ch/grants/grant/167125
Project lead: Sebastian Hiller | University of Basel

A new rapid and reliable bacterial phenotypic diagnostic technique detecting bacterial susceptibility to antibiotics using optical fibers
https://data.snf.ch/grants/grant/167137
Project lead: Sandor Kasas | EPFL

Novel targeted bacteriophage endolysin-based approach for treatment of drug-resistant Staphylococcus aureus infections
https://data.snf.ch/grants/grant/167037
Project lead: Martin Loessner | UETH Zurich

Fast Assessment of antibiotic resistance in bacteria by using nanomechanical arrays
https://data.snf.ch/grants/grant/177354
Project lead: Ernst Meyer | University of Basel

Anti-biofilm therapy using Local Application of Bacteriophages
https://www.jpiamr.eu/projects/antibio-lab/
Project lead: Patrice Nordmann | University of Fribourg

Ecosystem- and genome-guided antibiotic discovery
https://data.snf.ch/grants/grant/167051
Project lead: Jörn Piel | ETH Zurich

Partnership against Biofilm-associated Expression, Acquisition and Transmission of AMR
https://www.jpiamr.eu/projects/beat-amr/
Project lead: Qun Ren | EMPA

Antimicrobial peptide dendrimers (AMPD) and bicyclic peptides (AMBP) as therapeutic agents against multidrug resistant bacteria
https://data.snf.ch/grants/grant/167048
Project lead: Jean-Louis Reymond | University of Bern

Rapid diagnostics of blood stream infections using synthetic nanobodies
https://data.snf.ch/grants/grant/177368
Project lead: Markus Seeger | University of Zurich

Fighting antimicrobial resistant infections by high-throughput discovery of biofilm-disrupting agents and mechanisms
https://www.jpiamr.eu/projects/disrupt/
Project lead: Jan-Willem Veening | University of Lausanne

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Recommended citation style
Markus Seeger et al.: NRP 72 Thematic Synthesis “Faster diagnostics and new therapeutic approaches”, Bern, National Research Programme “Antimicrobial Resistance” (NRP 72), Bern.

72 NRP Antimicrobial Resistance
National Research Programme

Swiss National Science Foundation

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Design and layout
Binkert Partnerinnen AG, Zurich

ISBN 978-3-907087-59-6

Swiss National Science Foundation

Swiss National Science Foundation (SNSF)
Wildhainweg 3, P.O. Box, CH-3001 Berne

www.snf.ch www.nfp72.ch