72 NRP
Antimicrobial Resistance
National Research Programme

OPTIMIZED USE OF ANTIBIOTICS AND BEHAVIOR CHANGES

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

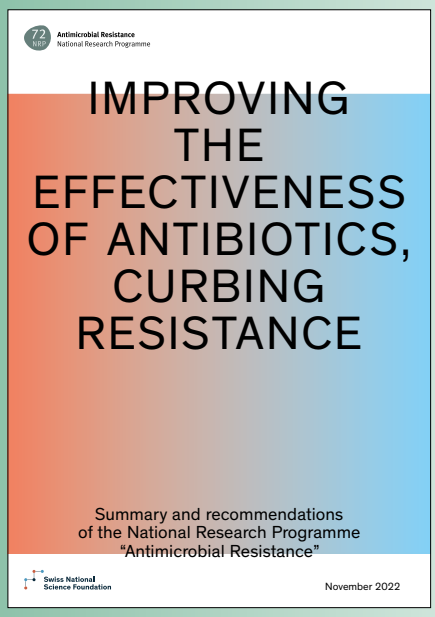
In addition, researchers synthesized their results on three overarching topics, corresponding to the three research modules of NRP 72:

- *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 the people involved). 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 Steering Committee of NRP 72 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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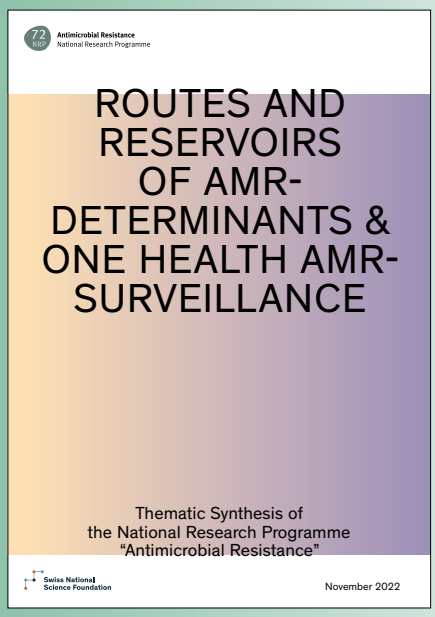
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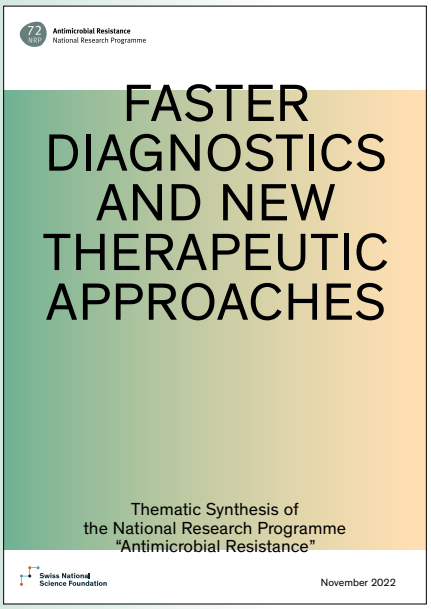
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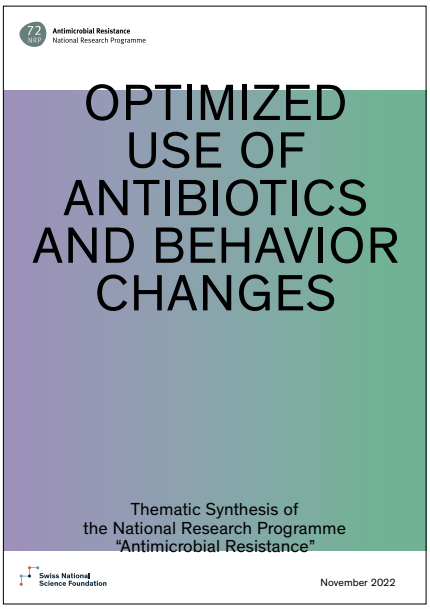
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Editorial

The growing resistance of bacterial pathogens against antimicrobial drugs constitutes a serious public health threat worldwide (Antimicrobial Resistance Collaborators 2022). The aim of the NRP 72 is to contribute to reducing the emergence, selection and transmission of antimicrobial resistance and mitigate its negative effects on the therapy of infectious diseases in both humans and animals. In view of the complexity of the problem, the research programme had been divided into three modules covering 1) the development and spread of bacterial resistance, 2) new antimicrobial drugs and diagnostic techniques, and 3) optimized use of antimicrobials and behavior changes. In the final stages of the programme, a multidisciplinary working group of NRP 72 researchers was constituted for each module with the mandate to merge the individual projects and their results into a comprehensive synthesis with practical impact for the overall conclusions and recommendations. The first task of each working group was to outline the current situation and challenges regarding bacterial resistance in Switzerland. Subsequently, the NRP 72 projects were closely scrutinized and discussed with the principal investigators in order to translate the results and insights of their research into an integrative set of recommendations for stakeholders, competent authorities and policy makers. Each working group appointed a coordinator responsible for leading the discussion and compiling a thematic synthesis in close exchange with the NRP 72 Programme Manager, with members of the Steering Committee and with the Head of Knowledge and Technology Transfer. To foster the integration and consensus building process, each working group was accompanied by a sounding board comprising reputed practitioners and scientific experts representing key stakeholders and interest groups. Feedback and inputs from the sounding board were sought regularly through all steps of the thematic synthesis process until finalization. Thereafter, key issues and recommendations were discussed with a wider circle of stakeholders to accommodate the heterogeneous needs of many actors with distinct economic, societal and political interests.

All persons involved in the working group, sounding board and NRP 72 Steering Committee are listed in the publication details at the end of this report. A big thank you goes to all of them for their always constructive and interesting contributions to the synthesis report and the underlying discussions.

Hanspeter Nägeli
Coordinator of the NRP 72 Synthesis Working Group
on “Optimized use of antibiotics and behavior changes”

Executive summary

Antimicrobial resistance is threatening our ability to treat human and animal diseases caused by bacterial pathogens. The aim of the NRP 72 is to contribute to securing the efficacy of antimicrobial agents against bacterial infections by developing new medicines or diagnostic tools, and by reducing the emergence, selection and spread of resistance. Module 3 supported this research programme by a threefold approach, i.e., by strategies that aim to optimize the use of antimicrobials, reduce the need for these drugs or limit the negative consequences of their administration in human and veterinary medicine. Different interventions were the focus of NRP 72 module 3 projects: antimicrobial stewardship (promoting the responsible use of antimicrobials), diagnostic stewardship (promoting diagnostic tools that guide the optimal and reduced use of antimicrobials), disease prevention (de-escalating the need for antimicrobials) and behavior changes (minimizing the risk of antimicrobial resistance transmissions).

A multidisciplinary working group was dedicated to merging the 15 different projects carried out as part of Module 3 and integrating the outcome of their research into a comprehensive synthesis leading to practical recommendations. This working group was supported by members of the NRP 72 management, by the Head of Knowledge and Technology Transfer and by members of the NRP 72 steering committee. In addition, the working group was flanked by a sounding board comprising reputed practitioners and scientific experts, whose feedback was sought throughout the synthesis process, particularly during the final drawing up of recommendations.

The working group has started by conducting an analysis of the current situation in Switzerland and came to the conclusion that antimicrobials are still prescribed with undue frequency in both human and veterinary medicine, i.e. in cases where they offer no or only marginal benefits. In many instances, antimicrobials are used with an unnecessarily broad antibacterial spectrum, in inappropriate combinations, in incorrect doses or for excessive duration. On the basis of this analysis, the working group considered that the risk of continued emergence, selection and spread of bacterial resistance can only be further mitigated by a One Health approach with the participation of a broad range of interest groups and stakeholders, including hospitals, professional organizations, health insurers, farmers' and consumers' organizations, the pharmaceutical and food industries, retailers, the gastronomic sector, medical and veterinary faculties, agriculture schools and the competent authorities. Training courses need to be organized and offered so that all persons belonging to these stakeholder and interest groups always have the highest possible level of knowledge with regard to measures that prevent the emergence of bacterial resistance.

In conjunction with the sounding board, the working group proposes general recommendations for interested target groups. First, NRP 72 findings should be considered and integrated into existing guidelines for the diagnosis and treatment of bacterial infections, including, e.g., the guidelines issued by the Swiss Society for Infectious Diseases. Widespread dissemination and promotion of these guidelines is needed to increase awareness among physicians in hospitals and primary care. Second, the One Health principle should be exploited by transferring knowledge and experience in one area (human or animal) to another. For example, new diagnostic tools developed in human medicine should be adapted for analogous challenges encountered in veterinary medicine. Conversely, the experience gained on monitoring and benchmarking of antimicrobial prescribing in the veterinary field should be helpful in developing similar strategies in human medicine. Third, antimicrobial and diagnostic stewardship interventions should be carried out in collaboration with the pharmaceutical industry, not only to accelerate the market introduction of new tests and drugs but also to protect the efficacy of antimicrobials already present on the market. In addition, new antimicrobial drugs

should be subjected to focused resistance surveillance after approval and their use should be continuously monitored. Finally, research on the societal impact and benefits of animal health programmes should be funded as a high priority.

The projects centred on the main topics of the NRP 72 module 3 translated into concrete recommendations for action as well as proposals for follow-up studies. The background, scope, target groups and expected benefits of these recommendations have been discussed with the involved stakeholders, first during meetings with the sounding board and then as part of an extended stakeholder dialogue meeting. A consensus could be reached on the following recommendations:

1. A procedure needs to be launched to ensure that hospitals allocate adequate resources for the development and implementation of tools for antimicrobial stewardship, diagnostic stewardship and patient information.
2. Antimicrobial prescribing in primary care should be assisted by user-friendly decision support guidelines and should be monitored and benchmarked systematically.
3. Diagnostic tests and consultation times promoting prudent antimicrobial use should be fully reimbursed.
4. Animal production systems that reduce the need for antimicrobials should be further supported. Incentives for “antibiotic-sparing” animal production should be launched and the market popularity of meat from “antibiotic-sparing” animal production should be promoted.
5. Veterinary herd health consultants should be trained, and an economic mechanism introduced that fully retributes their herd management services.
6. The risk of importing bacterial resistance through international trade of animal products should be reduced by encouraging low- and middle-income countries to implement principles that optimize and reduce the use of antimicrobials in farm animals.

We would like to thank all members of the sounding board and participants of the extended stakeholder dialogue meeting for their highly valued input and the in-depth discussion on these proposed recommendations.

1

Introduction: Current situation and challenges regarding the use of antimicrobials in Switzerland

Chapter summary

Any use of antimicrobial drugs favours the acquisition, selection and spread of bacterial resistance. However, antimicrobials are frequently prescribed even when they offer no or only marginal benefits and, in many instances, antimicrobials are used with an unnecessarily broad antibacterial spectrum, in inappropriate combinations, in incorrect doses or for excessive durations. To minimize bacterial resistance and thus secure the effectiveness of antimicrobial drugs, a One Health approach is required that involves all stakeholders and interest groups (hospitals, physicians, veterinarians, farmers, the pharmaceutical and food industries, retailers and the gastronomic sector, health insurers, patients and consumers). This can be achieved by an assessment of the target groups' needs, perceptions, and psychosocial determinants, followed by the development and evaluation of fit-to-purpose interventions. Three types of interventions are the focus of the module 3 NRP 72 research: antimicrobial stewardship (promoting the prudent use of antimicrobials), diagnostic stewardship (promoting diagnostic tools that guide the optimal and reduced use of antimicrobials) and disease prevention (to de-escalate the need for antimicrobial drugs), including behavior changes that reduce the risk of resistance transmissions.

1.1 Current situation

The use of antimicrobials in human and veterinary medicine and the development of bacterial resistance are intrinsically linked in the context of an evolutionary arms race. Any antimicrobial administration in humans and animals favours the selection of resistant bacteria in the microbiota. Antimicrobial use is also viewed as the main driving force for the spread of bacterial resistance among both humans and animals (Butaye et al. 2014, Cusini et al. 2010, Fleming-Dutra et al. 2016, Holmes et al. 2016). Many organizations, countries, pharmaceutical companies, and other stakeholders are taking measures to combat the public health threat of bacterial resistance against antimicrobial drugs. The World Health Organization (WHO) launched a global action plan to ensure the prevention and treatment of infectious diseases with safe and effective medicines (https://www.who.int/health-topics/antimicrobial-resistance). This initiative against the surge of bacterial resistance is endorsed by many international organizations, including the Food and Agriculture Organization of the United Nations and the World Organization for Animal Health (https://ec.europa.eu/health/system/files/2021-04/ev_20210325_co05_en_0.pdf), by the European Union (https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance_en) and by national authorities around the world (for example the Centers of Disease Control and Prevention of the United States: https://www.cdc.gov/drugresistance/index.html). In the private sector, an alliance of pharmaceutical companies has been founded to preserve the efficacy of existing antimicrobial drugs and to create incentives for the development of new drug classes (https://www.amrindustryalliance.org/our-members). In Switzerland, too, many efforts have been undertaken to prevent the development and spread of bacterial resistance, particularly as part of the Swiss Strategy on Antibiotic Resistance (StAR; https://www.star.admin.ch/star/en/home.html). For almost 20 years, the Swiss Centre for Antibiotic Resistance (ANRESIS) has been providing surveillance data on the prevalence of bacterial resistance and the consumption of antimicrobial drugs in humans (https://www.anresis.ch). However, an analysis of the current situation shows that there is a continued need for further measures to safeguard effective antimicrobial agents both in human and veterinary medicine.

1.2 Need for interventions in human medicine

Antimicrobial drugs have dramatically changed the prognosis of many severe infections, including bacterial pneumonia, that were associated with high mortality in the pre-antibiotic era. Also, many advances of modern medicine, for example surgical procedures and organ transplants, would not be possible or would be more

perilous without antimicrobial agents. However, there is an inherent trade-off between treating patients with antimicrobial drugs to ensure optimal clinical outcomes and preserving the effectiveness of antimicrobials for future generations. Unfortunately, the bounded rationality of human minds makes it difficult to adequately assess such benefit-risk scenarios, and therefore antimicrobial drugs are frequently prescribed "just in case it helps", without taking into account the consequences of their use (Teixeira Rodrigues et al. 2013, Krockow et al. 2019). Accordingly, the overuse of antimicrobial drugs (i.e. the use of antimicrobials when they have no or only marginal benefits) as well as their misuse (e.g., the use of drugs with unnecessarily broad spectrum or for excessively long durations) are still common both in the outpatient and the inpatient setting worldwide.

Overall, 90% of the volume of antimicrobial agents is prescribed in the outpatient setting (Zanichelli et al. 2018). Despite the fact that Switzerland has relatively low antibacterial drug use compared to other European countries, i.e. 9.1 defined daily doses per 1,000 inhabitants per day (DID) in 2019 compared to the European median of 18.4 DID (country range: 8.9–32.4), there is still considerable potential for improvement (Swiss Antibiotic Resistance Report 2020). Sociocultural factors are important determinants of prescribing, as there is a marked difference of antimicrobial use between linguistic regions in Switzerland, the German-speaking part having the lowest antibiotic consumption (7.9 DID) compared to the Italian-speaking (11.6 DID) and the French-speaking parts (12.6 DID). 50% of antimicrobials are prescribed for respiratory tract infections, 25% for urinary tract infections and 10% for skin infections.

A study in Switzerland assessed the self-reported drug prescribing of 250 primary care physicians (selected from the 60% top antibiotic prescribers) for 9961 patients with diseases commonly resulting in antimicrobial use (Glinz et al. 2017). A high proportion of these patients received antibiotics for conditions for which these drugs are rarely indicated. This was the case for 70% of the patients with acute otitis media, for 47% of patients with acute rhinosinusitis, for 44% of patients with tonsillitis/pharyngitis and for 42% of patients with acute bronchitis. Compared to other European countries, Switzerland is also known for a high frequency of fluoroquinolone use in the outpatient setting (Plate et al. 2020), although this antibiotic class is strongly implicated in the emergence and spread of resistance (Cizman et al. 2018, Swiss Antibiotic Resistance Report 2020) and is included by the WHO on the watch list of antimicrobials that should be prescribed only for specific indications (https://www.who.int/publications/i/item/WHOEMPIAU2019.11).

According to a survey, the majority of the Swiss population is informed about the potential negative impact of resistance against antibiotics. Most people are aware that the unnecessary use of antibiotics decreases their effectiveness and therefore tend to accept a medical decision of not prescribing an antimicrobial agent (Demo SCOPE, 2020). The outcome of this survey thus suggests that patients are not the major barrier to reducing antibiotic prescriptions. There are other factors that might put pressure on general practitioners to prescribe antibiotics, including consultation time (prescription of antibiotics to terminate a consultation; Akkerman et al. 2005, van der Zande et al. 2019) and concerns about missing a threatening bacterial disease such as pneumonia, sepsis or other severe infections. Diagnostic tools with limited accuracy and long turnaround times, for example in the assessment of urinary and respiratory tract infections, are not suited to adequately supporting physicians in their decision on whether or not to treat with an antimicrobial drug (Llor & Bjerrum 2014, Mylotte 2021). Inappropriate use of antibiotics also remains frequent in Swiss hospitals. For example, in surveys of antibiotic use at University Hospital Basel during 2017 and 2018, 182 out of 548 prescriptions (33%) were deemed inappropriate, with 83 prescriptions (15%) not adhering to guidelines and 59 (11%) with an improper indication (Gürtler et al. 2019).

In conclusion, while the glass may be "half full" with regard to the quantity and quality of antimicrobial drug consumption in Switzerland compared to other countries, there is still ample room for improvements in the prescribing of antimicrobial drugs and behavior changes among physicians and the public (Piezzi et al. 2020, Barnsteiner et al. 2021, Ramette et al. 2021, Renggli et al. 2021a). This can be achieved by generating new evidence-based data, recommendations, and interventions such as continued education on prudent antimicrobial use, by assisting physicians in the prescribing of antimicrobials through guidelines and decision support systems, by providing sufficient consultation times, and by offering guidance on the use and implementation of appropriate diagnostic tools (Drekonja et al. 2015). Unfortunately, many hospitals in Switzerland

do not dedicate specific resources to antibiotic stewardship programmes. Other countries have regulations in place that mandate hospitals to fulfil minimal criteria for antibiotic stewardship (Beovic et al. 2018).

Until recently there were few national treatment guidelines for infectious diseases in Switzerland, an issue that has been addressed by the Swiss Society of Infectious Diseases since 2017 in the context of the Swiss Strategy against Antibiotic Resistance (StAR). Existing guidelines target hospital and primary care settings and are easy to access (https://ssi.guidelines.ch). However, only a minority of primary care physicians are aware of these recommendations, which therefore need to be disseminated and promoted more intensively. When implementing guidelines, diagnostic tools, or other interventions, it is crucial to provide continuous feedback to physicians and to gain a nationwide overview of the overall impact of such measures.

1.3 Need for interventions in veterinary medicine

Antimicrobial drugs constitute an important pillar in the treatment of animals affected by bacterial infections and are essential for public health objectives to combat the transmission of zoonotic infections. The decision to apply antimicrobials is influenced not only by animal health and welfare considerations, but also by economic constraints, especially in the case of farm animals. Unfortunately, in the short run, it may still be cheaper to treat with broad-spectrum antimicrobials than to run appropriate diagnostic tests and introduce effective preventive measures (Hubbuch et al. 2021).

To reduce and optimize antimicrobial use in veterinary medicine, various countries and organizations have developed guidelines adapted to national or local requirements (see for example Swedish Veterinary Association 2009, Holloway et al. 2013, British Cattle Veterinary Association 2015, European Union 2015, British Small Animal Veterinary Association 2018, Federation of European Companion Animal Veterinary Associations 2018, Jessen et al. 2018). These guidelines apply both to farm and companion animals. In Switzerland, the ban of antimicrobial growth promoters since 1999, coupled with joint efforts of veterinarians, animal breeders, farmers (promoting herd management, vaccination programmes and disease eradication) and competent authorities (introducing new drug regulations and electronic record obligations) led to a notable reduction of antimicrobial use in animals (Gesellschaft Schweizer Tierärztinnen und Tierärzte 2017, Bundesamt für Lebensmittelsicherheit und Veterinärwesen 2019). In the context of the Swiss Strategy against Antibiotic Resistance (StAR), guidelines for the prudent use of antimicrobials in cattle and swine have been available since 2016, and there are meanwhile also guidelines for the prudent use of antimicrobials in small and exotic animals.

The sale of antimicrobials for farm animals dropped by around 50% in Switzerland between 2010 and 2019, mainly due to lower prescriptions of orally administered medicated premixes, while sales of antimicrobials exclusively registered for companion animals dropped by around 15%. The use of highest priority critically important antimicrobials (HPCIAs), according to the WHO classification based on their relevance for human medicine, has also been drastically reduced since 2016 (https://www.blv.admin.ch/blv/de/home/tiere/tierarzneimittel/antibiotika/vertrieb.html). One main indication for antimicrobial treatments are diseases in calves that are physiologically particularly vulnerable to bacterial infections, whereby treatments are often given to prevent the spread of disease in calf fattening or rearing operations. For respiratory diseases, which is the most frequent reason for antibiotic use in calves, a trend towards decreased antimicrobial treatment intensity has been observed over the last years. The production type heavily influences antimicrobial consumption. In large commercial herds with 200 or more fattening calves per year, an average of 30 days of antimicrobial treatment per calf and year was observed in 2011–2012, but this value dropped to 8.7 days per calf and year in 2016–2017 (the lifetime of each animal being around 4 months). In small- to mid-sized operations, the average number of days with antimicrobial treatment per calf and year was 21 days in 2014 and 7 days in 2016–2017 (Beer et al. 2015, Lava et al. 2016, Schnyder et al. 2019). A reduction in the use of antimicrobial agents was also found for pigs. Between 2011 and 2015, the overall estimated number of antibiotic therapies for pigs in Switzerland dropped by 30% with a decrease of 64% in the use of colistin, a

decrease of 16% in the use of 3rd- and 4th-generation cephalosporins and a decrease of 7% in the use of macrolides (Stebler et al. 2019). In this context, the impact of animal health programmes has been documented across 291 pig farms (Echtermann et al. 2021). Currently, population-adjusted antimicrobial sales for food-producing animals in Switzerland are lower compared to neighbouring European countries, but still higher than in Sweden, Norway and Finland (European Medicines Agency 2020). Currently, population-adjusted antimicrobial sales for food-producing animals in Switzerland are lower compared to neighbouring European countries, but still higher than in Sweden, Norway and Finland (European Medicines Agency 2020).

Bacterial strains resistant to antimicrobial drugs are frequently detected in farm animals. For example, *Escherichia coli* expressing extended-spectrum ß-lactamases (ESBL) or methicillin-resistant *Staphylococcus aureus* are found in rectal and nasal swabs, respectively, of calves and pigs (Huber eßt al. 2010, Hausherr et al. 2019), and high resistance rates against tetracyclines are common among respiratory tract pathogens (Pipoz et al. 2016, Schönecker et al. 2019). Unfortunately, HPCIAs are still often prescribed in food-producing animals, especially in calves (Gonzalez et al. 2015, Fertner et al. 2016, Hubbuch et al. 2021). Fluoroquinolones were applied in 65% and 3rd- and 4th-generation cephalosporins in nearly 10% of single-animal treatments in calves in large fattening operations in Switzerland (Beer et al. 2015). In smaller farms, fluoroquinolones and 3rd- and 4th-generation cephalosporins were used in almost 40% and 5%, respectively, of the treatments (Lava et al. 2016). This inappropriate use of antimicrobials in animal production is associated with an increase in resistance rates (Schönecker et al. 2020, Lüthi et al. 2021) and thus raises concerns regarding the potential transfer of antibiotic resistance along the food chain and into the environment.

The antimicrobial drugs used in companion animals, including horses, are not to be neglected, as the close contact of pets with owners facilitates the transmission of resistant bacteria (see for example Rossi et al. 2019). In addition, the trend for intensive medical care of dogs and cats poses a risk for nosocomial infections and is associated with an increasing number of geriatric and immunosuppressed patients who are highly susceptible to infections with multidrug-resistant bacteria. The potential transmission of resistant bacteria from companion animals to humans underlines the need for prudent antimicrobial use in horses, small animals, and exotic animals (Guardabassi et al. 2004, Paul et al. 2011, Guardabassi et al. 2013, Grönlund Andersson et al. 2014, Prescott & Boerlin 2016). HPCIAs are frequently administered to companion animals (Murphy et al. 2012, De Briyne et al. 2014, Buckland et al. 2016). For example, for convenience reasons, 3rd-generation cephalosporins are widely used, in the form of a single injection of a long-acting formulation (Hardefeldt et al. 2017 and 2018, Singleton et al. 2017, Hopman et al. 2018). Surveys conducted as part of the NRP 72 reinforce the notion that compliance with prudent use guidelines remained limited in veterinary medicine (see the “AntibioticScout.ch” project). This makes it clear that further measures are needed to ensure the sustainable use of these drugs. Considering the explicit One Health consequences of antimicrobial administrations in animals, a practical guide for dog and cat owners has been produced, which contains background information on multi-resistant bacteria in companion animals and explains measures that need to be taken by pet owners to reduce the risk of transmission of such bacteria to humans (Heim et al. 2020).

1.4 Current challenges

To a considerable extent, the same classes of antimicrobial drugs are used for human and animal patients. Antimicrobial resistance can also be transferred among humans and animals by various routes. Because over-prescription of antimicrobials is common in both human and veterinary medicine, a One Health approach is required to combat bacterial resistance (Sarrazin et al. 2017, McEwen & Colligno 2018, Van Cleven et al. 2018). In a trade-off between short-term benefits and long-term risks, it is important to counterbalance the individual and immediate advantage of an antibiotic treatment with the longstanding detrimental consequences of increased resistance rates. All interest groups and stakeholders, including physicians, veterinarians, farmers, the food industry and laypeople (i.e. patients and consumers), should be engaged in adopting

strategies that reduce the emergence, selection and spread of resistant bacteria. It is therefore important to understand how antimicrobial resistance is perceived by all and what solutions they propose to control this problem, for example through disease prevention. For the rapid implementation of new knowledge, it is essential to continuously review the available evidence and the impact of interventions on antimicrobial use, and to update guidelines accordingly.

In high-income countries like Switzerland, poor adherence to prudent use guidelines is not the consequence of a lack of awareness, as physicians and veterinarians recognize antimicrobial resistance as a serious threat (Busani et al. 2004, De Briyne et al. 2013). However, physicians and veterinarians are influenced by similar factors when it comes to antimicrobial prescription decisions, i.e. pressure by their clients (patients or animal owners), lack of confidence in the available diagnostic tools, practical feasibility criteria and moral obligations to their patients (Coyne et al. 2014, McIntosh & Dean 2015, Speksnijder et al. 2015). Unlike physicians, who do not benefit from their prescriptions, veterinarians retain a profit margin on the drugs they sell. Although controversially discussed, it is suggested – based on experience in other countries – that removing this incentive could help to further reduce antimicrobial use in animals.

These issues highlight the importance of training and timely feedback on the impact of new measures. Indeed, veterinarians from six European countries, including Switzerland, reported a strong intention to prescribe antimicrobials responsibly in pigs and to support farmers in their effort to reduce the need for these drugs (Visschers et al. 2015, 2016a and 2016b). Farmers, on the other hand, have a lower awareness of antimicrobial resistance and related risks (Friedman et al. 2007, Marvin et al. 2010, Moreno 2014). Pig producers tend to be less worried about antimicrobial resistance than other risks of farming and generally estimate their antibiotic use to be less than that of comparable farms in the same country. Farmers appreciate the benefits of antibiotics, such as low cost, easy application and immediate treatment effect. Farmers' intention to reduce antibiotic use thus depends on their perception of the benefits of antimicrobials in animal production and their limited willingness to change production methods. Farmers generally attribute the responsibility for prudent antimicrobial use to their peers or to veterinarians rather than to themselves (Coyne et al. 2014). A survey of stakeholders in Swiss veal production (dairy farmers, veal producers, traders, slaughterhouse managers, advisors and veterinarians) revealed that all actors express a high level of awareness of the need to reduce antimicrobial use in meat production (Rell et al. 2020). However, the respondents requested that other antimicrobial-consuming sectors, such as human medicine, companion animal medicine, or consumers, take more responsibility in the problem-solving process. This observation confirms the phenomenon that when a group of people or organizations face a problem, each individual displays a strong tendency to blame others and assume that the others will take responsibility – so no one takes action. This behavior is also known as the bystander effect, or diffusion of responsibility (Darley & Latané 1968). In the aforementioned recent survey by Rell et al. (2020), the respondents agreed that large-scale production systems that favour transport and crowding of young calves from different dairy farms are mainly responsible for antimicrobial overuse and misuse in veal production. However, stakeholders believe that this type of production is irreplaceable due to the far-reaching specialization and mutual dependency of dairy and veal producers, thus giving little room for alternatives. Mirroring the bystander effect, participants in a survey conducted in the United States believed that they, as patients, and the general public are less responsible for causing antibiotic resistance problems compared to healthcare providers, scientists and drug companies (Worthington et al. 2020).

Various surveys have also been carried out to investigate laypeople's awareness and perception of antimicrobial resistance in a medical setting (Gualano et al. 2015, McCullough et al. 2016). These studies revealed that the overall public knowledge about antimicrobial resistance and its consequences is low, especially in countries with lax antibiotic market regulations (Grigoryan et al. 2007). A frequent misconception is that antibiotics are effective against viruses (Finch et al. 2004, Andre et al. 2010). The process of antimicrobial resistance development is also unclear to many people, and another frequent misconception is that the human body can become resistant or immune to antibiotics, thus failing to associate antimicrobial resistance with bacteria (Brookes-Howell et al. 2012, McCullough et al. 2016). The concept of resistance devel-

opment is often misunderstood, as many people believe that only the frequent use of antibiotics or the premature termination of an antibiotic treatment results in resistance. Many do not seem to be aware of the fact that even the adequate use of antibiotics can result in resistance. Probably as a consequence of this low understanding of the problem, many people do not believe that they are personally at risk and assume that the primary cause of resistance is poor hygiene in hospitals (Hawkings et al. 2007). Hence, the responsibility for preventing antimicrobial resistance is attributed to others. Similarly, persons preparing food for cooking do not seem to be aware of the potential exposure to resistant bacteria in their own kitchen, nor about its negative consequences (Kennedy et al. 2011). Therefore, to raise consumers' commitment to adopt resistance prevention during food preparation, their risk perception in relation to safe food handling should be improved. Also, most pet owners are not aware of the risk factors for zoonotic infections, the mechanisms of transmission, or specific measures to prevent transmission of antibiotic-resistant bacteria (Stull et al. 2012, Zanzani et al. 2014), although recommendations to minimize such transfers of zoonotic agents between pets and humans have been developed (National Association of State Public Health Veterinarians 2013, Lambertini et al. 2016).

In conclusion, there is a need for comprehensive action to reduce the risk of exposure to antibiotic-resistant bacteria. It is proposed to develop targeted messages for the prescribers of antimicrobials and the different groups of antimicrobial users (Smith et al. 2015). Interventions built on a structured approach, starting with an assessment of the target groups' determinants of behavior, including internal factors (e.g., needs, perceptions and knowledge) as well as external factors (e.g., legislation and seasonality), have been shown to be more likely to result in significant behavior changes (Huttner et al. 2010).

2
Focus of thematic synthesis

Chapter summary

Three types of complementary interventions are the focus of the NRP 72 Module 3 research to reduce the need for antimicrobials and promote optimized and more responsible prescribing of antimicrobials: diagnostic stewardship, antimicrobial stewardship and other behavior changes, including prevention measures. In this chapter, these three fields of action are briefly explained.

2.1 Diagnostic stewardship

Diagnostic laboratories provide clinicians with information on microbial pathogens and their susceptibility patterns. Biomarkers such as procalcitonin have additionally emerged as a useful guide for the need of antimicrobial treatments in the hospital setting (Schuetz et al. 2011). Diagnostic stewardship refers to the fit-to-purpose use of laboratory testing to improve antimicrobial use and treatment outcomes, optimize the use of diagnostic tests in specific clinical situations and limit the development and spread of antimicrobial resistance (Patel & Fang 2018, Septimus 2018). Diagnostic stewardship helps to decide which samples and diagnostic procedures are needed, and which group of human/animal patients will benefit from the testing. The advantages of testing include the identification of pathogens and their spectrum of drug susceptibility, potentially allowing the replacement of broad-spectrum antimicrobials with more narrow-spectrum agents. Diagnostic testing – such as biomarkers used as surrogate indicators of a bacterial or viral etiology – may facilitate the early discontinuation of antimicrobials or avoid their use altogether. There is a substantial deficit of validated diagnostic tools in veterinary medicine, which is due on the one hand to the complexity of diverse animal species and, on the other hand, to the distinct requirements for the treatment of groups (herd management) compared to the treatment of individual conditions. In particular, the lack of rapid diagnostic tests may preclude more prudent use of antimicrobials. Conversely, an overuse of diagnostic tests may cause unnecessary costs, and both overuse and underuse of such tests may lead to incorrect diagnosis and inappropriate treatments. Therefore, diagnostic stewardship contributes to the selection of the right specimen and the right test for the right human/animal patient at the right time to optimize and minimize the use of antimicrobial drugs.

2.2 Antimicrobial stewardship

Antimicrobial stewardship refers to multidisciplinary programmes designed to optimize the selection, dosage and duration of antimicrobial treatments in order to improve the clinical outcome while minimizing unintended consequences, including the emergence and selection of resistances (Ma et al. 2019). Stewardship programmes involve a coherent set of measures including improved education, prevention of infections, vaccination programmes, surveillance of antimicrobial resistance, control of health care-associated infections and the propagation of responsible antimicrobial use (Dyar et al. 2017, Septimus 2018, Renggli et al. 2021b). Responsible antimicrobial use is achieved by selecting the right drug, dose, duration of treatment and route of administration when antibiotics are needed. In human medicine, antimicrobial stewardship has gained attention in Switzerland in the hospital setting, although its implementation is still largely insufficient. A survey among 63 Swiss hospitals in 2016 showed that only 18 of them (29%) took advantage of a stewardship programme supported by the Federal Office of Public Health (Osthoff et al. 2017). The development of antimicrobial stewardship is even less advanced at the primary care level.

The vast majority of antibiotic treatments in veterinary medicine take place in private practices or private clinics that are comparable to primary care in human medicine. Accordingly, antimicrobial stewardship programmes in veterinary medicine aim to optimize antimicrobial prescribing in multiple settings, ranging from small private practices to large public hospitals. Their focus lies on maintaining the effectiveness of available antimicrobial agents by reducing the demand for antimicrobials, by promoting their responsible use, by

providing evidence-based alternative treatments and co-therapeutic approaches, and by restricting the prescription of HPCIAs (Trevisi 2014, Guardabassi & Prescott 2015, Lhermie et al. 2016, Lloyd & Page 2018). As part of the Swiss Strategy against Antibiotic Resistance (StAR), online tools assisting veterinarians with prudent antimicrobial therapy in a broad range of animal species have been available since December 2016 (https://www.vetpharm.uzh.ch/abscout).

2.3 Other behavior changes including prevention measures

The prescription of antimicrobial drugs is increasingly regulated as a condition for their market approval or in the form of additional restrictions. Nevertheless, much room still exists in the implementation of behavior changes by means of incentives that reduce the demand for antimicrobials, preferably by disease prevention, and support their responsible use. To reduce antimicrobial use in the agricultural sector, it has, for example, been proposed to raise a user fee on sales of antimicrobials for non-human use (Van Boeckel et al. 2017). Various target groups are to be addressed for the implementation of effective behavior changes, including physicians, veterinarians, farmers, pharmaceutical companies, patients and consumers. It is, however, crucial to establish the acceptance and effectiveness of such incentives.

One way to promote the prudent use of antimicrobial agents is to raise awareness among physicians and veterinarians about the overall costs and risks of antimicrobial treatments, including their socio-economic implications. In parallel, it is necessary to optimize knowledge and trust in the performance of diagnostic tests through appropriate training. Benchmarking approaches (where prescribers can compare their antimicrobial use against corresponding regional or national averages) could be deployed as a further incentive to promote the responsible use of antimicrobials by hospitals as well as medical and veterinary practitioners, without penalizing physicians/veterinarians with patients or animal groups at higher risk (like, for example, general practitioners with mainly elderly patients, or referral veterinary clinics seeing mostly critical patients). A mandatory Information System on AntiBiotics in Veterinary medicine (with the acronym IS-ABV) was introduced in 2019 as a surveillance instrument for the optimal and prudent use of antimicrobial drugs in veterinary medicine (https://www.blv.admin.ch/blv/de/home/tiere/tierarzneimittel/antibiotika/isabv.html), but its impact on the prescribing practice has yet to be determined. Yet another option is to provide solid and practical evidence that antimicrobial use on farms can be decreased by optimizing production chains without jeopardizing animal health, animal welfare or profitability. Incentives could also be offered to motivate the pharmaceutical industry to develop new antimicrobial agents and to support the restrictive use of these drugs once they get market approval. Finally, information campaigns can be launched to change the behavior and expectations of patients and consumers.

3

Scientific contributions to overcome existing challenges

Chapter summary

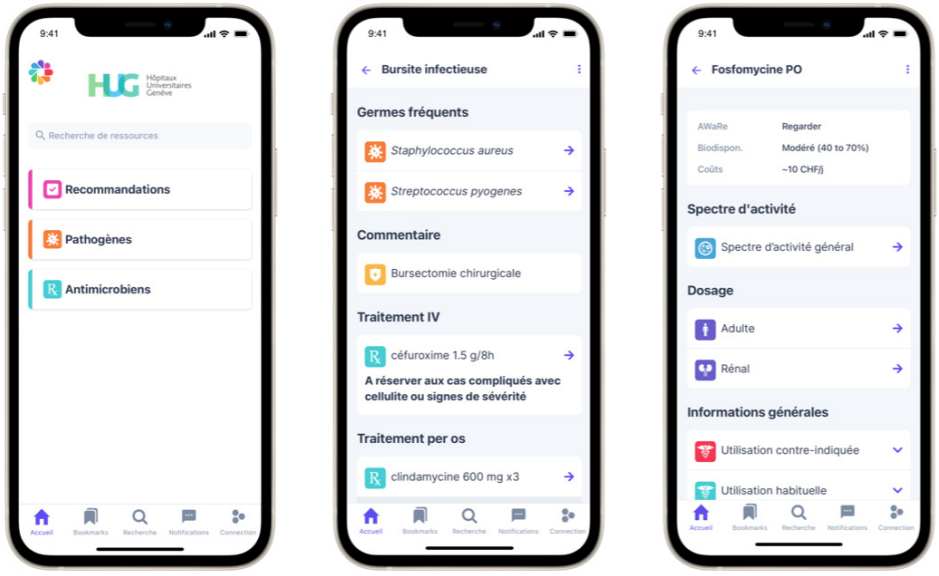
A total of 15 projects were carried out in the context of the NRP 72 Module 3, with the aim of optimizing and de-escalating the use of antimicrobial drugs and minimizing the emergence and transfer of bacterial resistance. Seven projects addressed antimicrobial and diagnostic stewardship and eight projects addressed the feasibility and effectiveness of behavior changes, including preventive measures. In line with the One Health design of the programme, this research covered a range of areas where bacterial resistance may emerge and spread: four projects were focused on the use of antibiotics in the hospital setting, two projects dealt with the prescribing of antibiotics in primary care and five projects dealt with antibiotic use in veterinary medicine. One project investigated precautionary actions that can be taken to reduce the risk of resistance transmissions in the community after hospital discharge, and another investigated how laypeople can avoid the transmission of resistances from animals or animal products. Yet another project investigated incentives for the pharmaceutical industry, and, finally, an overarching study investigated the effectiveness of intervention strategies. This chapter presents the main outcomes of these studies. The topics of antimicrobial and diagnostic stewardship overlap strongly and are therefore presented together, followed by research on other measures, including disease prevention.

3.1 Research on antimicrobial and diagnostic stewardship

“Compass” and “AB-assistant”

During a hospital stay, 30–50% of human patients receive antimicrobials. The appropriate prescribing of these drugs is challenging because new resistances are constantly emerging and the epidemiological situation varies geographically, but new information technologies could support physicians in their treatment decisions. *Benedikt Huttner* and colleagues at the University Hospital of Geneva developed computer-based decision support aimed at reducing and optimizing the prescription of antimicrobials in hospitals. In the COMPuterized Antibiotic Stewardship Study (acronym: COMPASS), an automated decision support was integrated with the in-house electronic health records and tested in a multicenter, randomized trial across three hospitals from September 2018 to February 2020. The intervention scheme provided support for the choice of antimicrobials as well as the duration of treatment, requested an accountable justification for deviations from the local guidelines, and included alerts for the re-evaluation of treatment choices as well as monthly feedback on prescribing practices (Catho et al. 2018, Catho et al. 2020, Catho et al. 2021, Ranzani et al. 2021). This intervention did not have any measurable impact on the overall level of antibiotic use, presumably due to an insufficient acceptance by physicians, suboptimal user friendliness and, at least in the included hospitals, a comparably low level of antibiotic use.

To explore ways to increase the user-friendliness and flexibility of digital stewardship tools, Benedikt Huttner participated in an international project (with hospitals in the Netherlands and Sweden in addition to Geneva) to develop and test, in a randomized/step wedge-controlled trial, a smartphone application (referred to as AB-assistant) aimed at improving the compliance of physicians with local prescribing guidelines.



"AB-Assistant" project: Interfaces of the AB-Assistant app for smartphones.

The trial results have not yet been analyzed, but this project demonstrates a high demand for such an innovative digital tool, particularly among younger physicians. Thus, the researchers invite hospitals across Switzerland to participate in future adaptations of the AB-assistant.

"CITrUS"

To determine whether antimicrobial treatment is necessary after surgery in proximity the urinary tract, *Hans-Helge Seifert* and colleagues at the University Hospital of Basel launched a randomized controlled trial (with the acronym CITrUS) across different urology centers in Switzerland and abroad (Speich et al. 2019). All enrolled patients receive the same intravenous antibiotics (trimethoprim/sulfamethoxazole) during surgery. Thereafter, group A is treated with placebo whereas group B receives the trimethoprim/sulfamethoxazole combination for three days, which is the standard preventive antibiotic after urinary tract surgery. The plan is to enroll 1500 patients and the overall aim is to explore whether non-inferiority is warranted for the single dose of antimicrobial prophylaxis vs. the standard three days of prophylaxis. The study is still in progress, but one benefit of the trial became apparent from the finding that the diagnosis of urinary tract infections was not conducted in a uniform manner across the participating centers. In the context of urinary tract diseases, however, the implementation of standardized diagnostic procedures is essential to adequately prepare patients for surgery and provide optimal care while reducing the use of antimicrobials. The trial also demonstrated the need for behavior changes by avoiding prolonged bladder catheterisation or other risk factors for infections such as residual urine or bladder stones. This is illustrated, for example, by the observation that, after a period of about 3 weeks, all catheterized patients display evidence of bacteria in the urine. Antimicrobial therapy is then started and continued after surgery, even though the patients probably only show contamination-related bacteriuria. An alternative approach would be to change the catheter preoperatively and collect a urine sample through this new catheter, thus avoiding the detection of contaminating bacteria and reducing the need for antimicrobial administrations.

"OPA: Feedback culture and the rational use of antibiotics in the hospital setting"

To evaluate the impact of clinical audits in reducing antibiotic prescriptions, *Laurence Senn* and colleagues at the University Hospital of Lausanne carried out a multicenter intervention study (designated "OPA" for Objectif Préservation Antibiotique) in 8 acute care hospitals of 4 cantons in Western Switzerland. The participating institutions included a large university hospital (canton of Vaud), two medium-sized hospitals (cantons of Fribourg and Valais) and 5 small-sized regional hospitals (Morges, Nyon, Yverdon, Riviera Chablais and Pourtales). Hospi-

tal units were allocated to either intervention or control groups. Weekly clinical audits were conducted by a tandem consisting of an infectious disease specialist and a senior physician in charge of the patients (https://www.objectif-preservation-antibiotiques.ch). A total of 9715 hospitalized patients were screened, 1684 (17%) of these received a highly critical ("protected") antibiotic. The auditing tandem proposed a modification of the antibiotic therapy in 24% of cases. The rate of inappropriate antibiotic use varied from 8% in intensive care units to 32% in surgical units, and from 15% for carbapenems to 38% for fluoroquinolones. In some hospital units, a decrease in the use of fluoroquinolones, 4th-generation cephalosporins and piperacillin-tazobactam was observed, but the prescribing of 3rd-generation cephalosporins and carbapenems remained unaffected. Besides raising the awareness on the problem of bacterial resistance, this project highlights the importance of a dedicated antimicrobial stewardship team to establish a feedback culture, provide continued education rounds and overcome barriers to the implementation of prudent use guidelines. Further benefits of the study are 1) an antimicrobial stewardship programme initiated in the participating university hospital, 2) prescription modules with automated alerting, and 3) the launch of a collaborative effort between the involved cantons to homogenize guidelines.

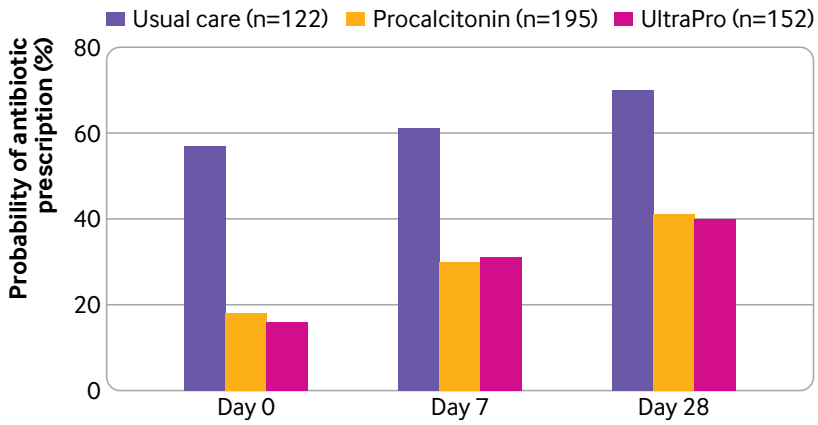
"OPA" project: Website of the multicenter "Objectif Préservation Antibiotique" intervention study, promoting antimicrobial stewardship, conducted at hospitals in Western Switzerland (screenshot, taken in November 2022).

"Faster screening benefits patients and may cut costs"

Rapid diagnostic tests are important not only to de-escalate antibiotic treatments but also to accelerate implementation of infection control measures targeting multi-resistant bacteria. Microbiological results are often delayed by traditional culturing methods, delaying implementation of isolation measures for patients carrying multi-resistant bacteria (and discontinuation of unnecessary isolation measures), thus causing additional financial burden to hospitals. To mitigate these problems, *Stephan Harbarth* and colleagues at the University Hospital of Geneva examined the efficiency of a rapid screening strategy based on the Loop-mediated isothermal AMPlification (LAMP) technique, directly applied on rectal swabs and stool cultures, to rapidly identify ESBL- and CPE (carbapenemase)-producing gut bacteria, and to inform infection control measures for critically ill patients. The investigators expected shorter turn-around times compared to conventional detection methods. The performance of the LAMP assay was compared to the conventional approach in a study involving approximately 1000 patients. The main outcome was that there is no benefit of using the LAMP assay directly on native stool samples. One of several reasons is that the poor predictive value of the LAMP assay increases the risk of implementing unnecessary isolation measures. Another explanation is that, before the start of the project, the hospital newly implemented full automatization of the diagnostic laboratory, thus substantially reducing turn-around times of conventional methods, which leads to underestimating the true benefits of the LAMP assay. For routine diagnostics, therefore, the researchers conclude that it might be more effective to accelerate culture-based methods rather then introducing novel, more expensive alternatives that are not yet thoroughly tested for their clinical benefit. It is worth noting that, culture-based methods have other advantages not considered in this study, such as species identification and storage for further investigations. It might, however, be advantageous to use rapid test methods to accelerate unit-wide surveys and contact screening during outbreaks.

“UltraPro: An algorithm to improve the diagnosis of pneumonia”

To improve the management of lower respiratory tract infections, *Noémie Boillat-Blanco* and colleagues at the universities of Lausanne and Bern monitored the use of an algorithm based on the point-of-care procalcitonin test and lung ultrasonography to guide antibiotics prescription in primary care patients. The impact of this intervention was tested in a cluster-randomized controlled trial conducted on 469 patients across 60 primary care practices in Switzerland (Lhopitallier et al. 2019). This study demonstrated that procalcitonin measured at the point of care reduced antibiotic prescriptions by day 28 compared to the usual care (40% vs. 70% of patients treated with antibiotics). There was no added reduction by sequentially performing lung ultrasound in patients with elevated procalcitonin (Lhopitallier et al. 2021). This diminished antibiotic use did not affect patients’ clinical recovery and satisfaction, and there was no increase in the healthcare-seeking behavior of study participants. Furthermore, the intervention drastically reduced the use of chest X-rays compared to the usual care (21% vs. 55% of patients subjected to X-ray). From these findings, the researchers concluded that the point-of-care procalcitonin test for managing lower respiratory tract infections can reduce antibiotic prescriptions without jeopardizing patient safety.

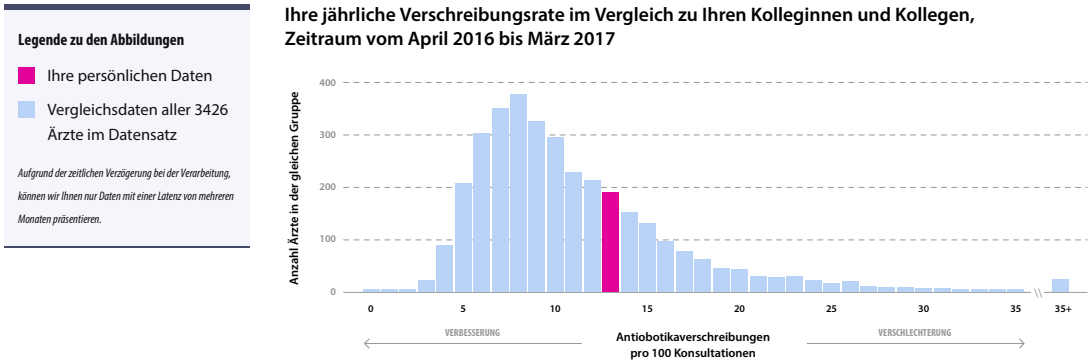


UltraPro project: Probability of antibiotic prescription by days 0, 7 and 28 in each study group (usual care, procalcitonin test only and UltraPro, i.e. sequential procalcitonin and lung ultrasonography tests). This study demonstrated that the procalcitonin test reduces antibiotic prescriptions in patients with respiratory tract infections (source: Lhopitallier et al. 2021).

As a further benefit of the study, general practitioners declared during interviews that with this simple diagnostic tool they felt empowered to make decisions to reduce antibiotic use. A health economic analysis also showed a similar cost between the two arms (usual care and point-of-care procalcitonin). Based on these results, the Swiss Society for Infectious Diseases has included the procalcitonin test in its guidelines for the management of pneumonia. However, successful implementation of procalcitonin point-of-care testing in primary care depends on its reimbursement by health insurers.

“Learning from claim data”

To test the impact of benchmark monitoring on the responsible use of antimicrobials, *Heiner C. Bucher* and colleagues at the University Hospital of Basel conducted a randomized controlled trial with 3426 general practitioners representing the 75% top antibiotic prescribers across Switzerland. The physicians’ identity was anonymized and not known to the investigators. The data were retrieved from routine claims of three health insurers covering 1,270,453 patients’ information, including 4,848,498 consultations. Every three months, primary care physicians in the intervention group received feedback on the number of antibiotics prescribed per 100 consultations, a population-adjusted benchmark comparison with other primary care physicians, as well as guidelines for the evidence-based use of antimicrobials in primary care (Glinz et al. 2021).

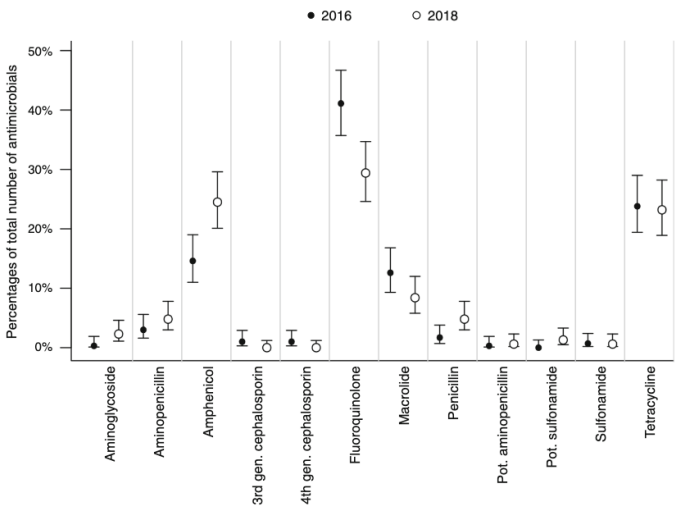


"Learning from claim data" project: Hypothetical example of three-monthly feedback to physicians with the number of antibiotics prescribed per 100 consultations and a benchmark comparison with other primary care physicians (source:Glinz et al. 2021).

The result showed a modest but not statistically significant reduction in overall antibiotic prescriptions between the second year of the intervention (2019) and the baseline year 2017. Only for quinolones were the antibiotic prescriptions in the second year of the intervention significantly reduced. In collaboration with ANRESIS, further analyses on the impact of this intervention on resistance rates associated with urinary tract infections are in process. This trial demonstrated that claim data are a valuable source of information to monitor overall antibiotic consumption at the primary care level and that the benchmarking of antimicrobial use would be applicable. However, the processing of data from a large number of insurance claims is resource- and time-consuming and should be facilitated by interoperable data collection, storage, and export formats. Systematic feedback to physicians in primary care does not appear to change antibiotic prescribing patterns, but more direct and focused feedback to general practitioners with high prescription rates might be more effective. Another recommendation ensuing from this trial is that if routine antibiotic prescription monitoring in primary care is implemented, this strategy should extend to large ambulatory centres and group practices.

"AntibioticScout.ch"

To mitigate bacterial resistance in veterinary medicine, *Hanspeter Naegeli* and his colleagues at the Vetsuisse Faculty Zurich and Bern carried out a computer-supported intervention to support prudent use recommendations issued in the context of the Swiss Strategy against Antibiotic Resistance (StAR). They launched the online tool AntibioticScout.ch to provide Swiss veterinarians with a user-friendly decision aid for the prescribing of antimicrobials (Peter et al. 2017 and 2018). The effect of this decision support system was tested by analysing medical records at the university teaching hospitals of Bern and Zurich and various private practices across Switzerland. One part of this evaluation was focused on selected diseases in calves (pneumonia, diarrhea and otitis) and confirmed the widespread use of antimicrobials in general and an excessive use of HPCIAs in these farm animals (Hubbuch et al. 2021).



"AntibioticScout.ch" project: Antimicrobials prescribed to calves in cases with pneumonia. Percentages of prescribed antimicrobial classes per total number of prescribed antimicrobials in 2016 and 2018 and corresponding 95% confidence intervals; gen., generation; pot., potentiated (source: Hubbuch et al. 2021).

The evaluation of antimicrobial prescriptions for selected canine diseases (acute diarrhea, urinary and respiratory tract infections as well as wound infections; Lutz et al. 2020) and selected feline diseases (acute upper respiratory tract diseases, lower urinary tract diseases and abscesses; Schmitt et al. 2019) also revealed a weak adherence to guidelines. Next, a comparison between 2016 (before the launch of AntibioticScout.ch) and 2018 (after the launch of AntibioticScout.ch) showed that antimicrobials were prescribed less frequently for specific indications and that the use of HPCIAs was diminished (Hubbuch et al. 2020, 2021, Lehner et al. 2020). However, the overall frequency of antimicrobial treatments did not change substantially between 2016 and 2018, and the use of HPCIAs remained widespread. This survey, therefore, highlights the need for further actions to secure a sustainable use of antimicrobials in veterinary medicine.

3.2 Research on other behavior changes including prevention measures

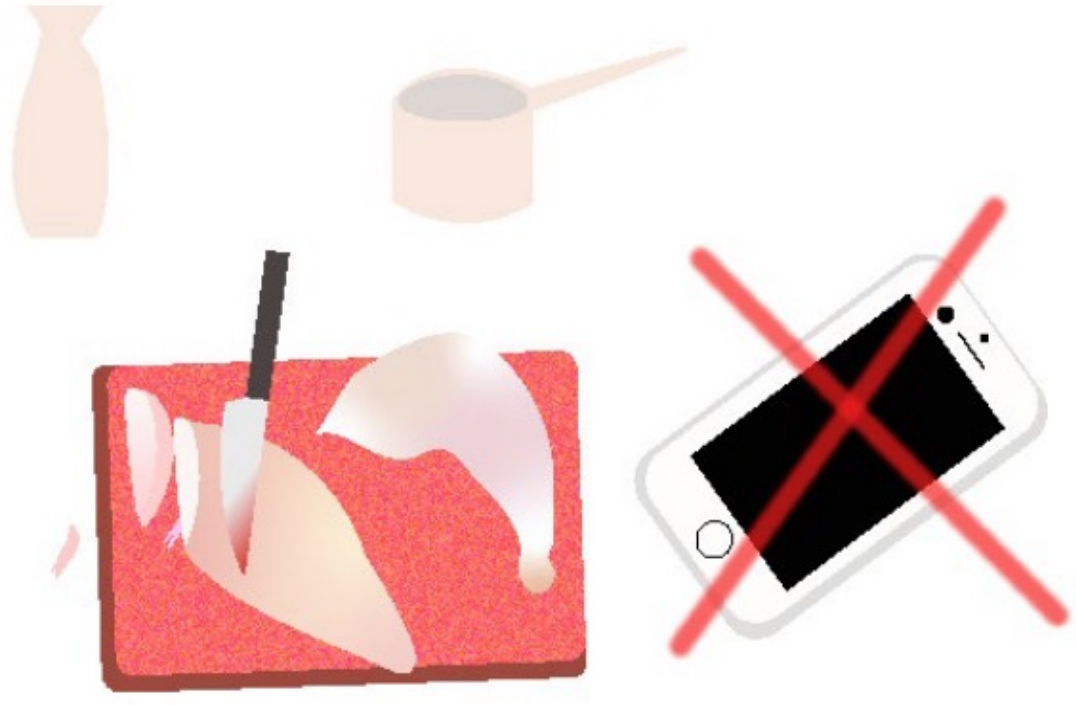
"MODERN"

To determine the rates and risk factors for the transmission of ESBL-producing bacteria within households, *Stephan Harbarth* and colleagues at the University Hospital of Geneva and abroad conducted a two-year prospective study (with the acronym MODERN) in 5 European cities. While transmission of ESBL-producing strains in the clinical setting has been extensively studied, our knowledge about the risk and pathways of their transmission in the general population is insufficient. Seventy-one previously hospitalized patients colonized with ESBL-producing *E. coli* (n = 45), *Klebsiella pneumoniae* (n = 20) or both (n = 6) were included in the study after hospital discharge. All participants (71 previously hospitalized patients and 102 household contacts) were monitored for 4 months with the collection of fecal samples. Whole-genome sequences of ESBL-producing bacteria were compared using pairwise single nucleotide polymorphism-based analysis. Transmission and acquisition rates were determined relative to the number of participants and the period at risk with potential exposure. The acquisition rate of ESBL-producing bacteria among previously negative household members was 1.9 per 100 participant-weeks at risk. Nineteen clonally related household transmissions were measured, translating to a transmission rate of 1.2 transmissions per 100 participant-weeks at risk. The identified risk factors included providing assistance for urinary and fecal excretion to the hospital-discharged persons. Essentially all transmissions took place during the first 2 months following hospital discharge (Riccio et al. 2021). This study highlights the importance of hygiene measures in community settings and could support behavioral interventions to better control the transmission of bacterial resistance in the community. A useful implementation would be 1) to inform patients that they are carriers of ESBL-producing bacteria at hospital discharge (which is currently not the regular practice), and 2) to hand out an information sheet to family or other household members explaining the improved hygiene precautions that should be taken.

"Ensuring safe food (and pet) handling"

Animal owners and consumers are exposed to resistant bacteria through contact with animals or animal products. To limit resistance transmissions, *Vivianne Visschers* and colleagues at the University of Applied Sciences and Arts, Northwestern Switzerland, developed interventions promoting a safe interface between animals and humans. First, a risk map depicting relevant exposure pathways between animals and humans was generated based on expert knowledge elicitation. Two relevant pathways of bacterial resistance transfer were identified: home processing of raw chicken meat and care of companion animals. Subsequently, laypeople were interviewed to describe their perception and attitude in relation to the two identified transmission

pathways. This research revealed psychological factors that need to be addressed in order to change the behavior regarding safe food handling in the household as well as pet handling (Freivogel & Visschers 2020 and 2021, Lechner et al. 2020). Strategies were developed and tested accordingly for their effectiveness in small-sized experiments. Educational illustrations and videos (see FHNW_Film2_V2_haustiere_klein-internet.mp4) and a goal-setting approach for optimal motivation increased laypeople's knowledge and awareness and influenced their behavior in a way to reduce the risk of animal-to-human transmissions of bacterial resistance.



"Ensuring safe food (and pet) handling" project: Cartoon illustrating that smartphones are bacteria traps. To avoid resistant bacteria landing on the smartphone and spreading further, it is important that the device remains outside the area used for the preparation of raw poultry, raw meat, raw fish or raw seafood. Hands should be washed thoroughly with soap and warm water before touching the smartphone after food handling (image taken from an educational video used in the project).

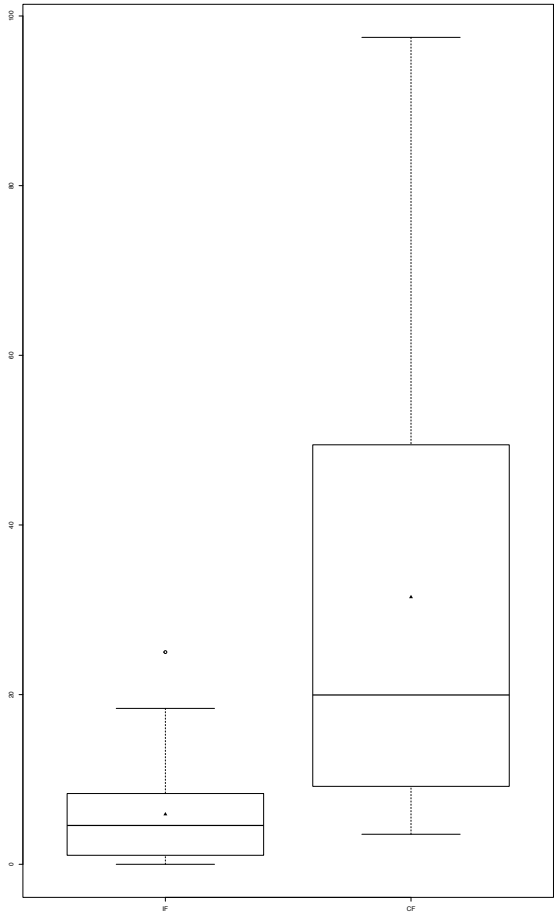
The effectiveness of these interventions was further confirmed in a longitudinal randomized control trial. It is pointed out by the researchers that interventions tailored to individuals' needs are especially well suited to increase the implementation of safe food handling among laypeople with little motivation. Veterinarians treating companion animals with antibiotics should discuss with their clients the problem of multi-resistant bacteria and how to prevent their transmission to humans.

"Providing the right incentives"

Different motivation scenarios targeting stakeholder groups (farmers, veterinarians, consumers) have been considered by *Stefan Mann* and colleagues at the Agroscope Reckenholz-Tänikon to de-escalate the use of antimicrobials in animal husbandry. By investigating the attitude of randomly selected farmers, they came to the conclusion that the main lever is to provide incentives that improve animal health, such that the reduction of infection diseases in animal production becomes a valuable side effect. Thus, current animal health and welfare programmes should be maintained and complemented with actions to further improve animal health in agriculture. Promising pathways include subsidies for regular veterinarian controls in stables to enhance animal welfare. The consequent improvement of animal health will diminish dependence on antibiotic treatments. A change of paradigm could take place by establishing a mechanism to reimburse comprehensive veterinary herd health consultancy services, which might lead to a further reduction in the prescribing of antimicrobials. The market may create additional incentives by introducing "antibiotic-sparing" products with a minimal need for the use of antimicrobial substances (Mann & van Aken 2021).

“The outdoor calf”

A new approach for disease prevention during veal calf fattening – usually associated with high metaphylactic and therapeutic antimicrobial treatments – has been explored by *Mireille Meylan* and colleagues at the Vetsuisse Faculty of the University of Bern. Based on previous analyses of risk factors for increased antimicrobial use and mortality in Swiss veal calf farms, they aimed to minimize the effects of management and housing factors leading to infectious diseases. Their strategy included the purchase of calves locally from neighboring farms, a quarantine period in individual hutches, timely vaccination of the animals against respiratory pathogens, followed by around 4 months of fattening outdoors in small groups (10 animals or less) in hutches with roofed, straw-bedded paddocks. This new concept was tested in a field trial with 19 intervention farms, which were compared with matched control farms over one year. Antimicrobial use in terms of treatment days was more than 5-fold and mortality 2-fold lower in the intervention farms compared to control farms. Daily weight gain was similar in both groups and animal health was increased in the intervention farms as signs of respiratory disease as well as lung lesions were detected less often in the intervention farms.



“The outdoor calf” project: Antimicrobial use reported as treatment incidence in defined daily doses (dd) per animal and year (ay). The mean antimicrobial use (triangles) was 5.3 times higher in control farms (CF) than in intervention farms (IF, outdoor veal calf). Horizontal lines, medians of antimicrobial use; boxes, low and upper percentiles; whiskers, minimal and maximal values (source: Becker et al. 2020).

Daily weight gain was similar in both groups and animal health was increased in the intervention farms as signs of respiratory disease as well as lung lesions were detected less often in the intervention farms. At the end of the fattening period, bacterial resistance in *E. coli* isolates was less frequent and the prevalence of multidrug-resistant *E. coli* was lower in intervention farms compared to controls. Economic analysis of profitability showed no relevant differences with traditional production systems (Becker et al. 2020 and 2021, Moser et al. 2020). This project demonstrates that relatively simple management measures achieve a drastic reduction of the need for antimicrobial treatments in a given sector – here veal fattening – without jeopardizing animal health. Prevention measures must start long before an animal becomes sick and requires treatment. The magnitude of the observed effects demonstrates that this approach has a high potential for reducing antimicrobial use. Similar strategies may also be evaluated in other animal production branches.

“Reducing antibiotic resistance in slurry”

Slurry and manure are used as organic fertilizers in agriculture. Particularly in pig and poultry farms, they carry antibiotic resistance determinants that may spread to the environment and build reservoirs from which clinically relevant antibiotic resistance could be transmitted to both animals and humans. Therefore, *Xaver Sidler* and colleagues at the Vetsuisse Faculty of the University of Zurich (together with researchers in five other countries) investigated methods to reduce both the quantity and variety of resistance in slurry and manure. Greenhouse chamber experiments and field tests were performed to determine the extent to which composting or anaerobic digestion can reduce resistance determinants. It was then investigated whether reducing resistance in organic fertilizers also reduces the number of resistance genes in environmental niches like soil. The hypothesis is that, by reducing or eliminating antibiotic resistance in organic fertilizer, it can be ensured that fewer resistance genes make their way into the food chain. The results of these studies are not yet available. Hence, this project could not be considered for the discussion of possible recommendations for action.

“Reducing antibiotic use in pig production in Thailand”

Increased awareness and antibiotic stewardship programmes are also urgently needed in low- and middle-income countries from which Switzerland imports animal products. With the goal of reducing antibiotic use in pig production in Thailand, *Thomas Van Boeckel* and colleagues at the ETH Zurich investigated the attitude and practices of pig farmers towards antibiotics in the Khon Kaen province. They also examined geographic relationships in the distribution of antimicrobial resistance genes. This project revealed that 63% of the farms display E. coli strains resistant to critically important antimicrobials and that the intensity of antimicrobial use was higher in large-scale than smallholder farms. There was a positive correlation between the proximity to drugstores, where antibiotics are sold over the counter, and the abundance of antimicrobials found on the farms, indicating that the ease of access to drugs may be an important driver for the development of antibiotic resistance. Instead, proximity between small-scale and large-scale farms was not a driver of antimicrobial spread between the two categories of farms (Hallenberg et al. 2020, Huber et al. 2021). This study, therefore, highlights the need to further study the role of veterinary drug suppliers, their potentially aggressive marketing for veterinary drugs and the lack of awareness of the problem of bacterial resistance in countries such as Thailand.

“Making healthcare systems resilient to antimicrobial resistance”

Considerable efforts are underway worldwide to combat the problem of antimicrobial resistance, but there is a need to understand which actions work under what circumstances with the overall goal of sustainable antimicrobial drug use. *Didier Wernli* and colleagues at the University of Geneva (together with partners in Sweden and Canada) identified factors making countries more resilient towards the growing challenge of bacterial resistance. They generated a comprehensive framework for an evidence-based assessment of interventions by describing the action goals, the sectors to be addressed as well as the settings (physical places where the intervention should be implemented), time frame, target groups and stakeholders in the One Health context (Léger 2021a). A database has been established to provide an overview of the measures available against the emergence and spread of resistances (https://amr-resilience.gtglab.net/database). The prospective analysis of several case studies allowed for the identification of factors that promote the sustainable use of antimicrobials and predict future dynamics of bacterial resistance. Important success factors include collaboration across disciplines, effective communication with actors and stakeholders as well as the role of the media. To strengthen the governance of bacterial resistance at a global level, the researchers advocate

the development of an international One Health platform for online learning (Wernli et al. 2020). The aim of this fully accessible and continuously updated platform is to generate scientific guidance on the design, implementation, evaluation and reporting of the wide range of possible interventions addressing the problem of antimicrobial resistance ("what works for whom and under what conditions") and allowing for an exchange of concepts and methods through online tools.

"Reconciling the profit motive with sustainable use of antibiotics"

The development of novel antimicrobial drugs is dampened by the poor financial perspective, particularly if a new effective product is kept back as a reserve antibiotic after its market introduction. How to reconcile the interests of pharmaceutical industry to maximize profits with the public health goal of minimizing antimicrobial resistance? To address this question, *Chantal Morel* and colleagues at the University Hospital of Geneva explored the feasibility of a finance-based intervention intended to re-align the profit motive of the pharmaceutical industry with the goal of prolonging the efficacy of new antimicrobial drugs through time. Unlike other industry incentives, the proposed scheme allows pharmaceutical companies to qualify for a financial bonus if the susceptibility of the target bacteria to their antibiotic product remains above a given threshold despite a certain minimum volume of drug usage. In theory, this antibiotic susceptibility bonus programme should help maximize efforts towards prudent prescribing practices and, therefore, minimize the risk of acquisition and transmission of antibiotic resistance (Morel et al. 2020 and 2021). Evidently, to be effective the bonus payments would need to exceed or at least equal the expected revenues from unimpeded sales (Rahman et al. 2021). On the other hand, such an incentive would encourage pharmaceutical companies bringing a new antibiotic to market to work with healthcare providers to optimize diagnostic stewardship, antimicrobial stewardship and divert resources previously spent on mass marketing to the appropriate use of their product exclusively against multi-drug resistant infections. This project emphasizes the need to include pharmaceutical industry as an active stakeholder in efforts to preserve the antimicrobial activity of newly developed drugs.

4
Recommendations for action

Chapter summary

The outcome of the NRP 72 research resulted in practice-oriented recommendations targeted at stakeholders and interest groups including competent authorities, hospitals, professional associations, health insurers, farmers' and consumers' organizations, the food industry, retailers, the gastronomic sector, veterinary faculties and agriculture schools. After discussing the insights from Module 3 projects, the working group and sounding board adopted general recommendations concerning both human and veterinary public health systems, followed by more specific advice for specific target groups. One set of proposed activities aims to strengthen antimicrobial stewardship, diagnostic stewardship and patient information in human hospitals. In the primary care sector, the recommendation is to introduce monitoring and benchmarking of antimicrobial consumption. In human medicine, there is a need to fully reimburse diagnostic tests and consultation times to support prudent antimicrobial uses. In the agricultural sector, the advice is to launch incentives for "antibiotic-sparing" methods of animal production, assisted by veterinarians trained as herd health consultants. Further recommendations deal with the risks associated with international trade and the societal benefits of animal welfare and health programmes. In addition, it's emphasized that continued education with a One Health approach is important so that stakeholders and interest groups always have the highest possible level of knowledge with regard to measures that prevent the emergence of bacterial resistance.

4.1 Discussion of insights from research

The problem of bacterial resistance against antimicrobial drugs was long considered a medical problem that can be solved by the rational prescribing of antibiotics in human and veterinary medicine and by the development of new drugs. Instead, NRP 72 research highlights the One Health complexity of this problem, which can only be tackled by a coordinated approach, including multiple human and veterinary health sectors as well as stakeholders in agriculture, the food industry and the pharmaceutical industry. It is also necessary to educate laypeople, including patients, animal owners and consumers, about the risk factors that may favour the transmission of bacterial resistance. In its effort to translate NRP 72 research into practical recommendations for action, the Module 3 Working Group followed the guidance of the project "Making healthcare systems resilient to antimicrobial resistance" (*Didier Wernli*), pointing out that the success of interventions against the surge and spread of bacterial resistance is fostered by effective communication between all stakeholders and actors. The involvement of the media is welcome in order to additionally communicate with the public, thereby increasing visibility and acceptability of the recommendations.

Many efforts to prevent the emergence and spread of bacterial resistance have already been made in Switzerland. Following a scoping review of the literature and an analysis of current statistics describing trends of antimicrobial consumption and resistance rates, however, the Module 3 Working Group concluded that there is a continued need for further measures to safeguard the long-term effectiveness of antimicrobial drugs (see Section 1.2). Several NRP 72 projects strengthened the working group's view that antimicrobial and diagnostic stewardship programmes need to be further developed and disseminated. For example, the project "OPA: Feedback culture and the rational use of antibiotics in the hospital setting" demonstrated the importance of a dedicated stewardship team in hospitals that provides feedback to physicians, offers continued education rounds and overcomes barriers to the implementation of prudent use guidelines. The "CITrUS" project disclosed a faulty procedure for the bacteriologic diagnosis of urinary tract infections leading to excessive antimicrobial administrations in hospitals, which could be avoided by adequately updating diagnostic guidelines.

The prevalence of bacterial resistance is intrinsically linked to the number of antimicrobial therapies applied in human and veterinary medicine. Therefore, it's important to generally optimize and de-escalate the use of these drugs in a One Health approach. To achieve this goal, NRP 72 research was centred on three types of interventions: antimicrobial stewardship (promoting the prudent use of antimicrobials), diagnostic

stewardship (promoting diagnostic tools that guide the optimal use of antimicrobials), and other behavior changes, including prevention measures (reducing the need for antimicrobials). The most important findings derived from NRP 72 research that trigger recommendations for action are briefly summarized below.

New insights concerning antimicrobial and diagnostic stewardship

The projects “COMPASS” and “AB-Assistant” in human medicine and the project “AntibioticScout.ch” in veterinary medicine emphasize the importance of employing user-friendly digital tools and devices to increase the popularity and effectiveness of antimicrobial and diagnostic stewardship programmes directed at physicians and veterinarians. An important insight resulting from the project “Faster screening benefits patients and cuts costs” is that it is both beneficial and feasible to accelerate conventional culture-based methods, primarily by automatization, to shorten turn-around times for the detection of antibiotic resistance. In terms of improving stewardship guidelines and introducing novel point-of-care diagnostic tests, the “UltraPro” project provides evidence that a simple point-of-care test can reduce the prescription of antibiotics in a cost-effective way without negatively affecting patients’ safety. Finally, the project “Learning from claim data” outlines a practical method, based on insurance claims, to monitor and benchmark antimicrobial usage in primary care. A brief synopsis of these projects is provided in Section 3.1. Their findings were the main driver for the development of recommendations aimed at further expanding antimicrobial and diagnostic stewardship programmes in primary care, in the ambulatory setting and in hospitals (see Section 4.2).

New insights into behavior changes including prevention measures

The “MODERN” project demonstrated that after discharge from hospital, patients are a potential source of hazardous resistance determinants that can be transmitted to family or household members. The project “Ensuring safe food (and pet) handling” identified relevant exposure pathways for resistance determinants transmitted from food or pet animals to humans. The project also involved the development and testing of interventions to ensure safe food and pet handling in households. The project “Providing the right incentives” compared different motivation scenarios to de-escalate the use of antimicrobials in animal production, with subsidies to further improve animal health considered to be the most promising strategy. The project “The outdoor calf” provides a proof of principle that effective disease prevention and de-escalation of antimicrobial use in animal production can be achieved, without any impact on profitability, by minimizing risk factors that threaten animal health and welfare. As an important outcome, the project “Reducing antibiotic use in pig production in Thailand” shows that increased awareness and stewardship programmes are also needed in low- and middle-income countries. Finally, the project “Reconciling the profit motive with sustainable use of antibiotics” highlights the need to include the pharmaceutical industry as an active stakeholder in the efforts to preserve the antimicrobial activity of marketed drugs. A brief synopsis of these projects is provided in Section 3.2. Their findings were the main driver for the development of recommendations aimed at de-escalating the use of antimicrobials in animals and reducing the risk of resistance transfer from animals to humans (see Section 4.2).

4.2 Recommendations for action

4.2.1 General recommendations

When discussing the results of the NRP 72 Module 3 research in relation to the current situation of bacterial resistance and the need for interventions in Switzerland (Section 1.2), the working group, in conjunction with the sounding board, adopted general recommendations directed at interested target groups.

- First, NRP 72 findings should be considered and integrated into existing guidelines for the optimal diagnosis and treatment of bacterial infections, including, for example the guidelines of the Swiss Society for Infectious Diseases. Updated guidelines of the Swiss Society for Infectious Diseases should be disseminated widely to increase awareness among physicians in hospitals and primary care. NRP 72 findings should also be taken into account for the further development of incentive systems for disease prevention in farm animals (e.g., BTS/RAUS programmes).

- Second, the One Health principle should be exploited by transferring knowledge and experience in one area (human or animal) to another. For example, new point-of-care diagnostic tools developed in human medicine should be adapted for analogous challenges encountered in veterinary medicine. Conversely, experience in monitoring and benchmarking antimicrobial use gained in the veterinary field should helpful in developing similar strategies in human medicine.

- Third, antimicrobial and diagnostic stewardship interventions should be carried out in collaboration with the pharmaceutical industry, not only to accelerate the market introduction of new tests and antimicrobial drugs but also to preserve the efficacy of antimicrobial drugs already present on the market. In addition, new antimicrobial drugs should be subjected to focused resistance surveillance after approval and their use should be continuously monitored. ANRESIS considers taking over this particular recommendation in its future surveillance plans.

- Fourth, research on the societal impact of animal health and disease prevention should be conducted to understand how to increase awareness on the benefits of animal health programmes. Indeed, the best approach to de-escalating antimicrobial use in farm animals is to strengthen incentives that prevent the spread of diseases (see the “Providing the right incentives” project). It is essential that both the public and policy makers understand the causal link between animal health, antimicrobial use, the prevalence of resistant bacteria, the risk of resistance transmission and consumer safety.

4.2.2 Specific recommendations

The projects centred on the main topics of the NRP 72 module 3 synthesis translated to specific recommendations for action as well as proposals for follow-up projects. The background, scope, target groups and expected benefits of these recommendations have been discussed intensively with all involved stakeholders, first during meetings with the sounding board and then at an extended stakeholder dialogue meeting. A consensus could be reached on the following proposals for action (three each for the human and animal sectors). The recommendations are formulated in general terms. However, the mentioned interest groups are advised to join forces to elaborate details and action plans (goals, implementation and timelines) for the proposed measures. An important aspect are the many new opportunities brought by digitalization, offering new user-friendly tools to improve antimicrobial and diagnostic stewardship in the human and the animal sector, both in primary care and the hospital setting.

Recommendation 1

Allocate resources for antimicrobial stewardship, diagnostic stewardship and patient information in hospitals.

Current efforts to implement antimicrobial/diagnostic stewardship and proactive patient information should be continued and expanded. A nationwide procedure needs to be launched that mandates hospitals to fulfil minimal criteria for antibiotic stewardship. Without such explicit requirements, it is unlikely that antibiotic stewardship programmes will be broadly implemented. Hospitals are also advised to develop and implement digital tools that facilitate antimicrobial stewardship, diagnostic stewardship and patient information.

Target audience: Directors and management of hospitals, including veterinary hospitals, Schweizerische Vereinigung der Spitaldirektoren SVS, H+ (Verband der Schweizer Spitäler), Swissnoso.

Initial situation/need for action: Despite a more prudent use of antimicrobial drugs in Swiss hospitals compared to many other countries, there is still ample room for de-escalation and optimization of antibiotic treatments (see Section 1.2).

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: The hospitals are advised to elaborate minimal requirements and consequently allocate the resources needed for adequate antimicrobial and diagnostic stewardship. The hospitals are particularly advised to develop and implement digital prescribing tools that also allow for prescription support, real-time surveillance of prescriptions, targeted interventions with specific treatment recommendations and the extraction of antibiotic consumption data at patient level level (see the “COMPASS”, “AB-Assistant”, “CITrUS” and “AntibioticScout.ch” projects). The hospitals are additionally advised to install sufficient tandem expert teams (consisting of a senior physician in charge of the patients and an infectious disease specialist) for regular audits and feedback concerning the appropriate use of antimicrobial drugs (see the project “OPA: Feedback culture and the rational use of antibiotics in the hospital setting”). Stewardship programmes should include training and continued education of all personnel. The “MODERN” project highlights the need to carefully inform patients (or animal owners in veterinary hospitals) when there is potential for bacterial resistances of concern to be carried into the community. Explicit guidance should be handed out on the precautions that need to be taken after hospital discharge.

Recommendation 2

Introduce monitoring and benchmarking of antimicrobial prescribing in primary care.

Health insurance claim data should be standardized to allow for the monitoring and benchmarking of antimicrobial use in the outpatient setting. Antimicrobial stewardship programmes targeting primary care should be developed and implemented.

Target audience: Federal Office of Public Health (FOPH) as the competent public health authority, Swissnoso, health insurers’ associations (Curafutura, Santésuisse), Swiss Medical Association, mfe Haus und Kinderärzte Schweiz, Swiss Academy of Family Medicine (SAFMED).

Initial situation/need for action: ANRESIS established a system for monitoring antimicrobial use in the

hospital and ambulatory care sectors. In contrast to the measures recently introduced in veterinary medicine, however, there is no system in place for the monitoring and benchmarking of antimicrobial drug use in the primary care sector in human medicine. The "Learning from claim data" project demonstrates that health insurance claim data can be a valuable source of information for monitoring overall antibiotic consumption at the primary care level and that a benchmarking of antimicrobial use is feasible. However, the processing of data from insurance claims should be facilitated by interoperable file formats. In addition, practitioners must be supported with appropriate decision aids aimed at the prudent use of antimicrobials.

Benefits of suggested change: With the proposed monitoring and benchmarking, prescribers would gain the possibility to review their decisions as to the use of antimicrobials and compare their prescriptions against corresponding regional or national references. However, a situation must be avoided where practitioners are blamed on the basis of such data. A nationwide benchmarking system is expected to optimize and reduce the overall use of antimicrobials.

Implementation: A possible strategy is to standardize insurance claims so that all data can be retrieved from interoperable databases of health insurers. The FOPH is advised to launch a national initiative in cooperation with health insurers, Swissnoso, the Swiss Medical Association and SAFMED to initiate the monitoring and benchmarking of antimicrobial use in primary care. The related experience gained in stationary/ambulatory care as well as in veterinary medicine might facilitate the implementation of appropriate monitoring and benchmarking tools. Standard formats for data exports from laboratories to ANRESIS should also be introduced (for example reporting of ZSR numbers) to allow for more efficient matching of claims and antibiotic resistance in primary care. Dedicated additional studies might be needed to monitor antimicrobial use for specific clinical indications.

Recommendation 3

Diagnostic tests and consultation times supporting prudent antimicrobial use in human medicine should be adequately reimbursed.

Diagnostic tests and patient consultations that optimize and/or reduce the use of antimicrobials should be integrated in prudent use guidelines, implemented, and fully reimbursed by health insurers. This includes both point-of-care tests and analyses carried out in medical laboratories. Analogous incentives for improved diagnostics in veterinary medicine are discussed in Recommendation 5.

Target audience: Health insurers' associations (Curafutura, Santésuisse), FOPH as the competent federal public health authority, health directors of the Cantons, Swiss Medical Association, mfe Haus und Kinderärzte Schweiz, Swiss Academy of Family Medicine (SAFMED), Swiss Society for infectious diseases.

Initial situation/need for action: An analysis of the current situation indicates that the decision to treat with antimicrobials is frequently not adequately supported by diagnostic tests. Antimicrobial drugs may also be given to avoid long patient consultations (see Section 1.2). Reimbursement for certain tests (CRP, leukocyte count) has been cut. Evidence for the advantages of appropriate point-of-care diagnostic testing is provided by the "UltraPro" project. Unfortunately, even if the clinical benefit has been demonstrated in randomized controlled trials, such diagnostic tests are not automatically eligible for coverage by health insurers.

Benefits of suggested change: Fit-for-purpose diagnostic tests help to optimize the prescribing of antimicrobials and reduce the need for these drugs, thus limiting the emergence and spread of bacterial resistance.

Implementation: The FOPH and health insurers are advised to fully compensate diagnostic tests and consultation times that have a scientifically proven effect on the prudent use of antimicrobials. The federal and cantonal authorities are encouraged to cover extra costs within the framework of infection prevention.

We recommend that the Swiss Infectious Disease Society updates its guidelines to incorporate new findings regarding the use of tests to guide antibiotic use. The Swiss Medical Association is advised to promote the dissemination of existing guidelines of the Swiss Society of Infectious Diseases to increase awareness among general practitioners.

Recommendation 4

Create incentives for “antibiotic-sparing” animal production systems.

Current animal welfare standards on farms should be further strengthened, particularly to improve disease prevention and animal health. In return, products (meat, milk and eggs) produced with healthier animals and thus with fewer antimicrobials should be rewarded by higher prices. In this endeavour, no false incentives should be created. For example, a situation must be avoided where that diseased animals are not treated adequately, as this would worsen animal welfare. Farmers and students at agricultural schools should be continuously informed about existing and newly emerging husbandry systems that rely on disease prevention rather than antimicrobials to maintain animal health and productivity. The market popularity of sustainable "antibiotic-sparing" products should be increased by educating consumers about societal benefits in terms of less bacterial resistance and resistance transfer to the environment and along the food chain.

Target audience: Swiss veterinary society GST, Food industry (Proviande, Fleisch-Fachverband), retailers (Coop, Migros, Denner, Volg, Lidl, Aldi), the gastronomic sector (Gastrosuisse), Swiss Farmers’ Union (SBV) and relevant sector associations, agricultural schools, consumer organizations, competent Federal Offices (Federal Food Safety and Veterinary Office (FSVO), Federal Office for Agriculture (FOAG), Federal Office of Public Health (FOPH)), competent authorities in the cantons, Nutztiergesundheit Schweiz (NTGS).

Initial situation/need for action: In conventional animal production operations, there is a high demand for antimicrobial agents, both to prevent the outbreak of bacterial diseases and to treat diseased animals. Using calf fattening outside the birth herd as an example, NRP 72 research shows that it is possible to significantly reduce the risk of infections and thus the need for antimicrobial agents without compromising on profitability (provided that the long-term investments for the required barn equipment are covered by financial incentives). Reductions of antibiotic use can be achieved through a multiplex strategy that includes adjustments in animal husbandry and production processes, vaccination programmes and antimicrobial as well as diagnostic stewardship measures (see the "The outdoor calf" and "AntibioticScout.ch" projects). However, calf fattening according to "The outdoor calf" is not immediately feasible because many legal requirements (environmental protection, spatial planning) cannot be met. Also, there are currently no sufficiently strong financial incentives for farmers to adapt their traditional production system to reduce the use of antimicrobial agents in animals (see the "Providing the right incentives" project).

Benefits of suggested change: Incentivizing animal production methods with improved animal health and correspondingly lower consumption of antimicrobial agents will reduce the risk of transferring bacterial resistance into the environment. Improved animal health will enable farmers to reduce antimicrobial use and thereby bring to the market products that are less likely to transfer antimicrobial resistance along the food chain. A strong incentive for "antibiotic-sparing" products could help farmers to modernize their production systems and further optimize animal health. To avoid creating wrong incentives, it is important that financial incentives are granted to farmers on the basis of improved animal health parameters rather than being coupled directly to the antibiotic consumption.

Implementation: The Federal Council is advised to integrate financial incentives for animal production systems that help to further de-escalate the use of antimicrobials into AP22+, which outlines the future agricultural policy in Switzerland. It will be necessary to grant subsidies for herd health consulting services

promoting disease prevention (see Recommendation 5). Obstacles to animal-friendly production systems such as disadvantages in obtaining subsidies ("Direktzahlungen") or lengthy building permit procedures for farms should be removed. Farmers' organizations and agricultural schools are advised to raise awareness among their members and students about existing and newly emerging husbandry systems, including biosecurity measures that reduce reliance on antimicrobials. Retailers and the gastronomic sector, together with consumer organizations, are advised to inform consumers about what could be achieved in terms of improving animal health and reducing the risk of resistance transfer if consumers paid a higher price for better quality.

Recommendation 5

Train veterinary herd health consultants (VHHCs).

Veterinary medicine students and veterinarians in Switzerland should be given the opportunity to be trained as VHHCs who can offer farmers an extended range of services. For that purpose, the existing "Fähigkeitsausweis Bestandesmedizin" (https://www.gstsvs.ch/de/beruf-bildung/weiterbildungstitel) should be relaunched, improved and considerably expanded with appropriate training, coaching and supervision programmes for veterinarians.

Target audience: Vetsuisse Faculty, FSVO and FOAG (as the competent federal offices), GST (as the professional organization of veterinarians), Nutztiergesundheit Schweiz (NTGS).

Initial situation/need for action: NRP 72 research shows, for example in veal calf fattening, that it is possible to substantially reduce the need for antimicrobials in animal production systems with targeted multimodal management measures to mitigate risk factors and optimize antimicrobial use (see projects "The outdoor calf" and "AntibioticScout.ch"). However, the expected reduction in antimicrobial sales would have a negative impact on the overall income of veterinarians and, particularly in the farm animal sector, veterinarians will not be able to offset these revenue losses without restructuring their business model. The problem is that farm health management and disease prevention are still not perceived as valuable as curative measures (Léger et al. 2021b).

Benefits of suggested change: A shift from individual (curative) medicine to more comprehensive veterinary herd health management focusing on preventive measures like, for example, biosecurity, hygiene, optimized vaccination schemes and advanced diagnostic tools will improve animal health. Strengthening and financially honouring the role of VHHCs also will reduce the dependence of veterinarians' revenue on antimicrobial sales.

Implementation: Changing the business model of veterinary practices requires improving the knowledge and training of veterinarians on herd health management. The Vetsuisse Faculty in collaboration with the FSVO and FOAG (as the competent Federal authorities) and the GST (as the Swiss Veterinary Association) are advised to adapt the veterinary curriculum by offering an expanded veterinary herd health track and to provide dedicated continued education programmes. An appropriate retribution system must be negotiated in advance with producer organizations and the competent authorities, because veterinary students and practitioners will only take advantage of this new professional track if they have a guarantee that they will be fully reimbursed for their services as VHHCs.

Recommendation 6

Address the risks associated with the international trade of animal products.

Target audience: FSVO, Swiss Agency for Development and Cooperation (DEZA).

Initial situation/need for action: It is not possible to solve the problem of antimicrobial resistance at national level alone. Farm animal health and welfare standards are also being promoted to different extents outside Switzerland. Nevertheless, as highlighted by the project “Reducing antibiotic use in pig production in Thailand”, the use of antimicrobial drugs and the problem of bacterial resistance are much more prominent in some low- and middle-income countries from which Switzerland imports certain animal products, including fish and seafood.

Benefits of suggested change: Lower use of antimicrobials abroad would allow products from abroad to be imported into Switzerland that are less contaminated with bacteria-harbouring resistance determinants, further reducing the risk of transferring such resistances to consumers.

Implementation: Competent federal authorities and Swiss delegates at international organizations such as the World Trade Organization are advised to strengthen the implementation of principles internationally that optimize and reduce the use of antimicrobials in farm animals analogous to the Swiss Strategy against Antibiotic Resistance (StAR). Focus should be placed on countries that export meat, fish or other animal products.

Overview on NRP 72 and JPIAMR projects on optimized use of antibiotics and behavior changes

Further and continuously updated information, including scientific publications, can be found for each project under the respective link to the SNSF Data Portal or JPIAMR website.

Procalcitonin and lung ultrasonography point-of-care testing to decide on antibiotic prescription in patients with lower respiratory tract infection at primary care level: Pragmatic cluster randomized trial
https://data.snf.ch/grants/grant/167133
Project lead: Noémie Boillat Blanco | Université de Lausanne

Routine antibiotic prescription and resistance monitoring in primary care physicians: A nationwide pragmatic randomized controlled trial
https://data.snf.ch/grants/grant/167066
Project lead: Heiner C. Bucher | Universität Basel

An interventional study to evaluate the impact of a rapid screening strategy in improving nosocomial ESBL and CPE control in critically ill patients
https://data.snf.ch/grants/grant/177454
Project lead: Stephan Jürgen Harbarth | Université de Genève

Aligning industry incentives with AMR control goals: Exploring the feasibility of an antibiotic susceptibility bonus for drugs to treat Gram-negative infection
https://www.jpiamr.eu/projects/asb/
Project lead: Stephan Jürgen Harbarth | Université de Genève

COMPASS study (COMPuterized Antibiotic Stewardship Study)
https://data.snf.ch/grants/grant/167079
Project lead: Benedikt Huttner | Université de Genève

Aligning industry incentives with AMR control goals: Exploring the feasibility of an antibiotic susceptibility bonus for drugs to treat Gram-negative infection
https://www.jpiamr.eu/projects/asb/
Project lead: Jürgen Harbarth | Université de Genève

A digital antimicrobial stewardship smartphone application to combat AMR: the AB-assistant
https://www.jpiamr.eu/projects/ab-assistant/
Project lead: Benedikt Huttner| Université de Genève

Potentials of incentive-based instruments to an animal-friendly reduction of antibiotics usage
https://data.snf.ch/grants/grant/166997
Project lead: Stefan Mann | Agroscope

A novel concept for veal calf production: “the outdoor veal calf”
https://data.snf.ch/grants/grant/167083
Project lead: Mireille Meylan | Universität Bern

AntibioticScout: Online tool for antimicrobial stewardship in veterinary medicine
https://data.snf.ch/grants/grant/167054
Project lead: Hanspeter Naegeli | Universität Zürich

Single-Dose Versus 3-Day Cotrimoxazole Prophylaxis in Transurethral Resection or Greenlight Laser Vaporisation of the Prostate: A Pragmatic, Multicentre Randomised Placebo Controlled Non-Inferiority Trial
https://data.snf.ch/grants/grant/177492
Project lead: Hans-Helge Seifert | Universität Basel

Implementation of routine audit and feedback on the use of protected anti-Gram-negative antibiotics: a multicenter, randomized trial using segmented regression analysis of interrupted time series
https://data.snf.ch/grants/grant/167192
Project lead: Laurence Senn | Université de Lausanne

Intervention of antimicrobial resistance transfer into the food chain
https://www.jpiamr.eu/projects/inart/
Project lead: Xaver Sidler | Universität Zürich

Piloting on-site interventions for reducing antimicrobial use in livestock farming in emerging economies
https://www.jpiamr.eu/projects/reduce-amu/
Project lead: Thomas Van Boeckel | ETH Zürich

Developing an evidence-based intervention for consumers to reduce the risk of multiple antimicrobial resistance transmission pathways
https://data.snf.ch/grants/grant/177456
Project lead: Vivianne Visschers | FHNW

Comparative assessment of social-ecological resilience and transformability to limit AMR in one health systems
https://www.jpiamr.eu/projects/amresilience/
Project lead: Didier Wernli | Université de Genève

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