



Joint Action  
Antimicrobial Resistance and  
Healthcare-Associated Infections

## Milestone 9.1

Gathering of national research priorities from at least five  
countries and gap identification

WP9 | Prioritizing and implementing research and innovation for public health needs

Leader acronym | INSERM, FHI

Author(s) | Yohann Lacotte, Marie-Cécile Ploy, Christine Årdal (*alphabetically ordered*)

Reviewer(s) | Sadika Bernard, Olivier Barraud

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# Gathering of national research priorities

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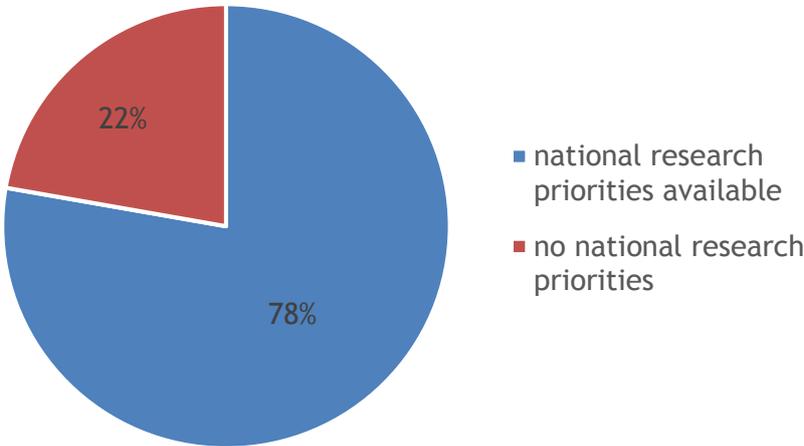
## Methods

WP9 partners were asked to extract research priorities from their national action plan and translate them into English.

Requests were sent to partners from nine different countries: France, Greece, Italy, Netherlands, Norway, Slovenia, Spain, Sweden and United Kingdom

## Results

Seven out of the nine countries sent back documents highlighting their national research priorities (all available in appendix).



Sweden and Italy did not report any research priorities at the time of our request.

# Gap identification

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## Methods

All reports from responding countries were analyzed by INSERM. This analysis led to the extraction of 38 research priorities clustered into 14 sub-topics.

Using this clustering, a mapping of the research priorities of the seven responding countries was analyzed for commonalities and focus. National priorities were then compared to JPIAMR's draft Strategic and Research Innovation Agenda (SRIA), which was made available for public hearing in August/September 2018.

Simultaneously an in-depth analysis was performed of one country's processes to identify research priorities. Norway was identified through discussions with JPIAMR as a country that had a strong focus on AMR research.

For further reading, national research priorities of each responding country are available in appendices. To make the reading easier, information used to build our mapping have been highlighted in different colors (one color associated with each of the 14 sub-topics identified, see table in the result part). The Norway case study is also available in Appendices.

## Results

**Table 1: Mapping of the research priorities of seven European country.**

### How to read this chart:

38 research priorities have been extracted from the documents sent by our partners.

Research priorities have then been clustered into 14 sub-topics (each associated with a different color).

A green cell means that a specific country (column) has identified a specific topic (row) as one of its national priorities.

Text in some boxes is meant to give information on each country specialty or top priority.

### Disclaimers:

This chart only represents the priorities explicitly addressed in the documents sent by our partners. A white box doesn't mean a country is not doing any research on a specific subject, but that this subject is not a priority in that country.

### Abbreviations:

AMR = AntiMicrobial Resistance

IPC = Infection Prevention and Control

UK = United Kingdom

		Country						
		France	Greece	Netherlands	Norway	Slovenia	Spain	UK
<b>Incentives</b>	<i>Work on new economic incentives or funding to foster research and innovation</i>	Others incentives		More funding	More funding		Other incentives	Other incentives
<b>Interaction</b>	<i>Work to encourage International/European research collaborations</i>							
	<i>Work to encourage private/public research collaborations</i>							
	<i>Work to encourage interdisciplinary research collaborations</i>							
<b>Structuring</b>	<i>Development of a “national steering committee” to structure and coordinate actions regarding AMR</i>							
<b>Development of new tools</b>	<i>Development of new antibiotic molecules</i>							
	<i>Development of new alternatives to antibiotics (vaccine, phages, antibodies, peptides ...)</i>							
	<i>Development of new diagnostic tools</i>							
<b>Fundamental research</b>	<i>Research on the bacterial mechanisms involved in resistance</i>							
	<i>Research on the causes and consequences of the appearance and dissemination of AMR</i>							
	<i>Other specific research unrelated to animals nor environment</i>	<i>Clostridium difficile</i>		membrane biogenesis, microbial ecology	continued carriage, microbial ecology			microbiome
	<i>Investigating new technologies to help developing antimicrobial molecules or diagnostic tools.</i>	artificial intelligence		synthetic biology				genomic technologies
<b>IPC in healthcare</b>	<i>Implementation, testing and evaluation of diverse IPC measures in the human health sector</i>	Research	Intervention	Research	Research	Intervention	Research	Intervention
<b>Antibiotic stewardship</b>	<i>Implementation, testing and evaluation of new measures for practitioner to improve their use of antibiotics</i>							
	<i>Research of new treatment strategies or ways of using known antibiotics (combination therapy, optimal dosing regimens, ...)</i>							
<b>Surveillance</b>	<i>Strengthen surveillance and monitoring of AMR (human, animal or environmental surveillance)</i>							
	<i>Develop new tools to facilitate the communication of surveillance data</i>							
<b>Training</b>	<i>Strengthen the training and education of practitioners (human/animal medicine) or patient</i>							
<b>Clinical trials</b>	<i>Research on how to create a high-quality clinical and laboratory trial network in Europe to optimize clinical trials</i>							
	<i>Development of cutting edge predictive technologies to assess how well a molecule might behave as a drug</i>			Organ on chip, zebrafish				

		France	Greece	Netherlands	Norway	Slovenia	Spain	UK
Socio-economic science	Improve knowledge of the critical aspects that lead to inappropriate use of antibiotics							
	Evaluate the socioeconomic consequences of antibiotic resistance							
	Evaluate the socioeconomic consequences of inappropriate antibiotic prescriptions (too much or too little antibiotics)							
	Improve knowledge of the quality of therapeutic care in primary and hospital care							
	Evaluate the impact of behavioural changes or interventional measures within and beyond the health care setting on AMR							
Animal sector	Research on the interaction of AMR with the veterinary sector (transfer of resistances between animals and humans, dissemination of resistances, ...)							
	Research of new antibiotics for use in veterinary medicine							
	Improve understanding of the critical factors that lead to a high consumption of antibiotics in farms							
	Evaluate the impact of food additives used in animal feeds (copper, zinc, coccidiostats, ...) on the AMR							
	Implementation, testing and evaluation of diverse IPC measures in the veterinary sector							
Environmental sector	Research on the interaction of AMR with the environment (transfer of resistances between the environmental bacteria and human pathogens, dissemination of resistances, ...)							
	Explore the effect of different drivers of resistance (disinfectants, biocides and heavy metals, ...) in nature							
	Explore the impact of fertilizers, especially manure, on the spread of AMR							
	Investigate the cost-effectiveness of cleansing environment measures							
	Implementation, testing and evaluation of diverse IPC measures in the environmental sector							
Food chain sector	Improve knowledge about the spread of resistance genes through food							
	Assess the need of new infection control measures in the overall food chain							
	Assess the need of new recommendation concerning kitchen hygiene and risk communication on food handling							

## Key messages:

Top priorities of participating countries:

- Fundamental knowledge on AMR (mechanism involved, causes, consequences, new targets, new technologies ...)
- Implementation of effective IPC measures, stewardship programmes and surveillance system

Important priorities of participating countries:

- Development of new antibiotics, alternatives to antibiotics or diagnostic
- Assessment of best practices and strategies for antibiotic stewardship
- Collaboration between the public and private sector, between different sciences or between countries
- Development of a “national steering committee” to structure and coordinate actions regarding AMR at national level

Research areas receiving medium priority:

- Research involving socio-economic sciences
- Research on incentives especially “non-push” incentives
- Research on how to improve the training of healthcare and veterinary practitioners
- Research on AMR in the animal sector
- Research on the cost effectiveness or best way to implement IPC measures

Research areas unmentioned or with little priority:

- Environmental sector still poorly addressed
- Food chain sector with almost no attention
- Research on how to improve clinical trials efficiency almost absent from research programs

The JPIAMR SRIA has a broad scope broken down into six thematic areas: diagnostics, environment, interventions, surveillance, therapeutics, and transmission. The SRIA and national research priorities strongly aligned, with the one exception of IPC measures where the SRIA is mostly silent.

Norway utilized comprehensive, ad-hoc processes to define its national AMR research priorities. The timing was aligned with the national strategy and action plan. Please see appendix for more detail. These processes could be difficult to duplicate in other countries. The case study also demonstrated that ad hoc processes may be successful.

## Conclusion

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The WP9 research priority mapping revealed three primary gaps in research priorities of participating countries:

- Research on AMR within the environmental field
- Research on the AMR within the food chain sector
- Research on how to improve clinical trials efficiency

Additionally, WP9 concluded with JPIAMR that an IPC research agenda was lacking and should be developed and integrated in relevant strategic research agendas. WP9 is currently developing this research agenda on HCAI & IPC to help addressing the lack of research on IPC measures.

# Appendices

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## Appendix 1 - France research priorities

The **French interministerial roadmap** for controlling antimicrobial resistance (National Action Plan) launched in November 2016 included 3 measures and 10 actions in the field of research and innovation (Part A).

One of these actions was to install a **strategic steering committee** for research on antimicrobial resistance. This steering committee has been created in France in September 2017 and has defined research priorities on AMR (Part B).

Moreover, the **French programme to prevent healthcare-associated infections (PROPIAS)** has also defined research orientations (Part C).

### A - Interministerial roadmap for controlling antimicrobial resistance - Research and innovation in the field of antibiotic resistance.

France is one of the world leaders in innovation relating to controlling resistance to antibiotics, thanks to the excellence of its research and the dynamism of businesses established in the country. Controlling antimicrobial resistance must involve **developing knowledge of how resistance to antimicrobial agents emerges and is transmitted**, as well as **developing new therapeutic and diagnostic solutions or alternative solutions to antibiotics**. Those objectives require:

- **Structuring research networks and observatories to strengthen research efforts;**
- **Encouraging better interaction between scientific, human, and social disciplines, and ensuring co-ordination of research efforts between the human-health, animal-health, and environmental sectors, steered by a transdisciplinary strategic council;**
- **Supporting and accelerating the transfer of research from the academic world to the industrial world by setting up a pro-active policy on public-private partnership and project support;**
- **Adapting new economic model applied to the development of new practices and products that enable resistance to antibiotics to be controlled.**

### CHALLENGE

- **Encourage access to and the availability of innovative products and new tools contributing to the control of antimicrobial resistance, by strengthening the structuring and co-ordination of research, as well as by encouraging academic / industry exchanges and by promoting products that contribute to controlling resistance to antibiotics.**

## MEASURES ADOPTED

### MEASURE 7 - Structure and co-ordinate research, development, and innovation efforts into AMR and its consequences

- Action no. 17: Install a strategic steering committee for research on antimicrobial resistance.
- Action no. 18: Set up a common intersectoral, interactive web portal identifying public and private actors as well as networks, laboratories, and research projects relating to AMR.
- Action no. 19: Strengthen and connect research and monitoring networks as well as observatories.
- Action no. 20: Strengthen research and innovation efforts. At national level, co-ordinate the scientific research program on antimicrobial resistance and related financing, while ensuring that the national effort is integrated with actions taken at European level (especially the JPI AMR), and by supporting research focused on public-health priorities.

### MEASURE 8 - Foster convergence between support for scientific research and innovation by strengthening public-private partnerships

- Action no. 21: Support and speed up transfers from the academic world to the industrial world in the field of antimicrobial resistance.
- Action no. 22: On a joint basis between academics and industrialists, set up regular exchange programmes by organising “academic / industry” meetings in the field of human and animal health, as well as the fields of agriculture, nutrition, and the environmental health.

### MEASURE 9 - Promote and preserve products that contribute to controlling resistance to antibiotics

- Action no. 23: Install a Comité Technique de l’Antibiorésistance (Technical Committee on Antimicrobial Resistance) in charge of giving opinions on the relevance of products to be used in human or veterinary medicine, and contributing to controlling resistance to antibiotics
- Action no. 24: Maintain the effectiveness of the therapeutic arsenal by adopting incentive measures that allow existing antibiotics to be retained in the market.
- Action no. 25: Provide innovative products and technologies contributing to the control of antimicrobial resistance with a set of regulatory and financial incentive mechanisms.

Action no. 26: Improve the use of in vitro diagnostic (IVD) tools contributing to control antimicrobial resistance, thanks to a better use of those technologies.

## B - Strategic steering committee - Research priorities on AMR.

In keeping with national and international initiatives and given that antibiotics are not the only option to counter antimicrobial resistance, the steering committee proposes, in a “one health” approach, to develop a national programme for research on antimicrobial resistance based on 3 pillars: research, development and innovation.

The aim is to gather skills from the French academic laboratories working in translational, fundamental and clinical research, and in the fields of public health, agronomic, environmental, and human and social sciences research, to federate them into an ambitious programme based on 4 interconnected interdisciplinary pillars in which man is not dissociated from its environment.

### 1) Emergence, transmission and dissemination of resistance

The study of biology in resistance mechanisms, their emergence, transmission (including the potential of resistance gene transfer between environmental bacteria and human pathogens) and their dissemination in the 3 ecosystems human, animal, environment- for a better understanding of the role of selective pressures, and to prevent and assess risks for human and animal health.

### 2) Therapeutic and preventive strategies to tackle antibiotic resistance

Development of innovative strategies including the most effective therapeutic approaches with limited risks of antibiotic resistance selection.

Approaches designed at controlling transmission (between bacteria and between hosts) of bacterial resistance in animal and human health and in the environment

Promoting development of alternatives/non-antibiotic strategies through vaccines development, probiotic approaches and new target identification.

### 3) Technological innovations to fight antimicrobial resistance

Intensify efforts in technological innovation (including artificial intelligence) for diagnosis, identification, and fast monitoring of resistance -in human, animal & environment. Critical for optimum treatment of patients and animals.

### 4) Antibiotic resistance: good clinical practices, public health, social, psychosocial, economic and legal issues

Relying on the study of social and psychosocial mechanisms and economic and legal matters related to bacterial resistance, this axis may be split in two major themes in human and animal health, and the environment:

- Obtain a better understanding of the societal and professional drivers of antimicrobial resistance, knowledge and risk perception, as well as barriers to and ways and means to counteract inappropriate antibiotic use
- Develop and assess innovative approaches to antibiotic stewardship and for controlling AMR

## C - Research orientations on healthcare-associated infections.

### 1) Develop prevention of hospital acquired infections (HAI) all along care pathways, involving patients and inhabitants

- Assess the impact of collective analysis of HAIs, interdisciplinary teamwork, mentoring on the quality of prevention of HAI and on the awareness of all professionals involved in patient care.
- Assess barriers to reporting HAI, their impact, and factors related to their removal.
- Assess the impact of patient-driven reporting.
- Look for relevant indicators for the community.
- Assess professional hazards and working standards in independent health professionals.
- Research relevant indicators for the care pathway.

### 2) Reinforce prevention and control of antimicrobial resistance in all healthcare sectors

- Assess bottlenecks related to reporting and the early implementation of recommended measures for superbugs (CPE and VRE).
- Assess, on national and regional levels, the logistic needs, costs (financial impact study, costeffectiveness ratio of interventions), and the consequences on the organisation of healthcare structures admitting patients with superbugs.
- Set interventional studies on the control strategies of diffusion of ESBL-producing bacteria in community and hospitals (including the management of *excreta*).
- Continue research on associated factors and prevention of *Clostridium difficile* infections.
- Intervention studies aiming at enhancing immunization coverage in careers (particularly against flu)

### 3) Reduce risks of infection associated with invasive procedures all along healthcare pathway

- Study the behavioral and organizational factors linked with the risk of surgical infections.

- Promote the use of data extracted from care structures dedicated to bone & joint infections.
- Improve research on analysis made from automated surveillance data of surgical site infections.
- Assess the impact of patients' involvement all along the care pathway on infection rates (surgical site infections, bacteremia on intravascular device...).

## Appendix 2 - Greece research priorities

AMR is an increasingly serious threat to global public health with a significant social and financial impact. Especially in Greece, during the last decade, a notable increase in the resistance rates of carbapenem resistant Gram-Negatives (CRGNs) isolates to tigecycline and colistin has been reported in several hospitals, where CRGNs are already endemic.

In an attempt to set up a strategy for AMR, in 2014, the Greek Ministry of Health and the Ministry of Agriculture have developed a total strategy for tackling Antimicrobial Resistance (AMR) at public health level. National strategies aim to control both the dissemination of CRGNs in healthcare settings through strict adherence to infection control measures and the prudent use of antibiotics either to the community and the agriculture or the healthcare facilities.

### I. HUMAN MEDICINE

#### A. HOSPITAL SECTOR

**National strategy goals are as following:**

1. To reduce AMR in health care settings and control the dissemination of CRGNs with specific target on Carbapenem-resistant Enterobacteriaceae.
2. To promote the rational use of antibiotics in hospitals (antibiotic stewardship programmes) in order to improve patient outcomes and patient safety, reduce AMR and healthcare cost.
3. To establish national surveillance systems for HAIs and antimicrobial use in health care facilities.
4. To organize and implement multimodal infection control programmes for the prevention and control of HAIs.
5. To strengthen local policies and reinforce hospital organization and management for prevention of HAIs.

**In 2014, a new institutional framework has been created and diffused in all Greek hospitals. The main, mandatory, axes of this framework, in hospital level, include:**

1. The establishment of Infection Control Committees and Antibiotic Stewardship Committees by qualified health professionals.
2. The formulation of an Infection Control Programme by each hospital in accordance with guidance issued by HCDCP (the Hellenic CDC).

3. The formulation by the Antibiotic Stewardship Committee of an Annual Action Plan that describes specific goals, actions and budget.
4. The monitoring of 9 indicators related to antimicrobial resistance and infection prevention and control of HAIs:
  - ✓ Incidence of BSIs due to targeted pathogens (CR-Acinetobacter baumannii, CR-Pseudomonas aeruginosa, CR-Klebsiella pneumonia, MRSA, VRE). Monthly.
  - ✓ Point Prevalence Surveys of HAIs and antimicrobial use. Every 2 years.
  - ✓ Surveillance of AMR in targeted antibiotics. Semesterly.
  - ✓ Surveillance of antibiotic use (DDDs). Semesterly.
  - ✓ Hand hygiene compliance. Every 2 years.
  - ✓ Alcohol based hand rub consumption. Annually.
  - ✓ Contact and Isolation Precautions compliance. Monthly.
  - ✓ Healthcare flu vaccination percentage. Annually.
  - ✓ Organizational and structural indicators (ex. staff ratio, number of beds, infection disease physicians, etc).
5. The continuous education and training of all healthcare professionals at the implementation of prevention and control measures.

## B. AMBULATORY SECTOR

National guidelines for the diagnosis and treatment of infections have been published since 2007 by the HCDCP in cooperation with the Hellenic Society for Infectious Disease. In 2015, an updated version and related training programmes have been introduced to primary healthcare physicians.

In late 2010, Greece also introduced electronic prescription in every day clinical practice. Nowadays, the e-prescribing platform provides also educational information.

## C. ONE HEALTH APPROACH

The main activities forward to this target include:

1. An established surveillance system for human medicine and veterinary.
2. A common data base on Salmonella infections. The reports are published.
3. An established Central Committee, in the Ministry of the Rural Development and Food, for the combat of AMR in accordance with the project of One Health Approach
4. An “One Health” Scientific Society is being founded to promote:
  - a. the collaboration of scientists between the relevant sciences
  - b. common SOPs and guidelines.

- c. the research in the field

## II. VETERINARY MEDICINE

The national policy for tackling AMR in veterinary medicine includes key actions which focus on:

1. Prudent use of antimicrobial agents. Their use in animals should be carried out only on the basis of veterinary prescription following the main principles of proper antibiotic use (antibiotics when strictly necessary and prescribed over a specific time at the appropriate dosage).
2. Education and training (workshops) of farmers, veterinarians and other professionals involved in the field of veterinary medicine / animal husbandry.
3. Reinforcement of the official control system for the distribution and appropriate use of veterinary medicines and medicated feed. All pharms and authorized pharmacies should keep detailed records of each incoming or outgoing veterinary medicinal product.
4. Strengthening the control of residues of veterinary medicines (antimicrobials) in live animals and animal products within the scope of the "National Residue Monitoring Plan".
5. Improving prevention and control of infections in animals by upgrading current health programs and promotion of good agricultural practices, vaccinations, encouragement of production and use autovaccine etc..
6. Strengthening the existing AMR surveillance systems in zoonotic bacteria and / or commensal microbial indicators and harmonizing data on the use of antimicrobial substances in accordance with Directive 2003/99 / EC and Decision 652 / 2013 / EU.
7. Developing and strengthening partnerships with Public Health Sector for the prevention and control of AMR.
8. Evaluation of the measures taken at national level concerning the fight against AMR. This will be a key responsibility of an Interministerial Committee which will be established by Ministry of Rural Development and Food and Ministry of Health, to coordinate any scheduled actions.

## Appendix 3 - Netherlands research priorities

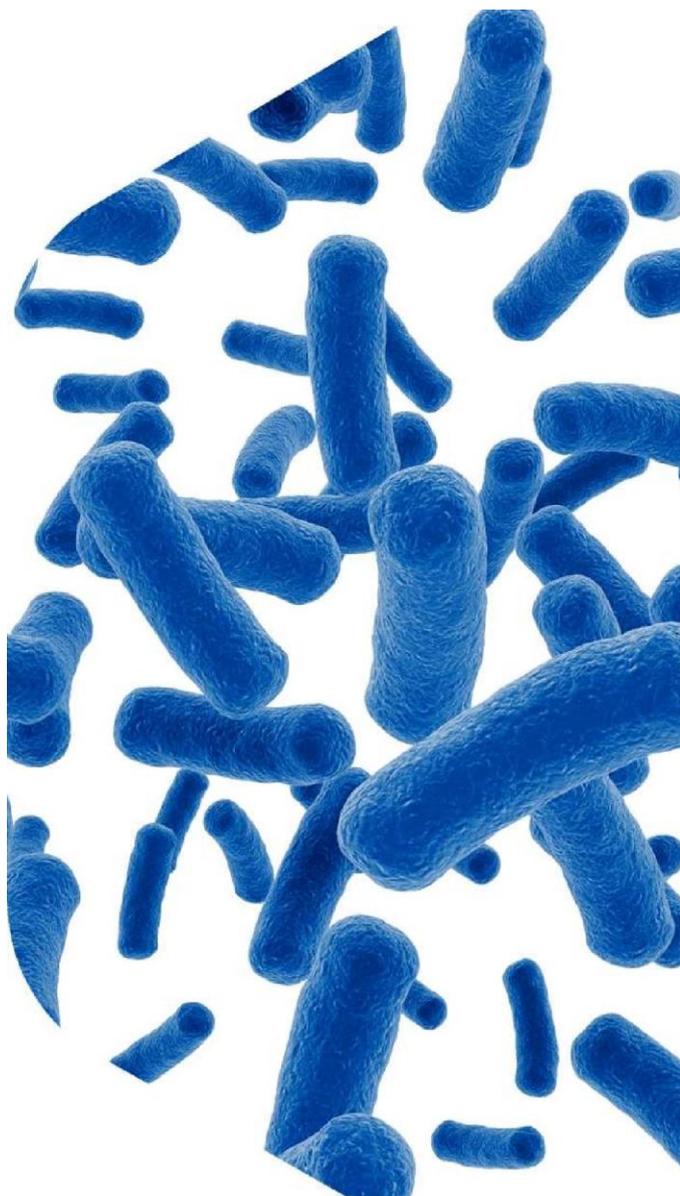
### 3-A Netherlands R&D agenda



netherlands antibiotic  
development  
platform

# Research & Development Agenda

Version 1.0 - 2018



## Background

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resistance is one of the most urgent and severe threats to global public health and economy. The discovery of penicillin in 1928 marked the beginning of the age of antibiotics, a revolution in healthcare that has been the cornerstone in decreasing the morbidity and mortality of major bacterial infectious diseases in humans and animals. The availability of antibiotics has played a pivotal role in reducing the impact of major bacterial infectious diseases, such as pneumonia and tuberculosis. However, from the moment that antibiotics were used commonly to treat infectious diseases, bacteria have developed resistance to them. Accelerated by the overuse of antibiotics in the 20th century, multiple drug-resistant (MDR) bacteria have emerged in all parts of the world. Well-known examples include pathogens of the so-called 'ESKAPE' class, namely vancomycin resistant Enterococcus (VRE), methicillin-resistant Staphylococcus aureus (MRSA) and multi-drug resistant (MDR) Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Escherichia coli; as well as among others Clostridium difficile and MDR and extremely drug resistant (XDR) tuberculosis (T B). Infections with these pathogens pose an enormous threat to human health and lead to massive costs for health care.

An important aspect of the global problem on AMR is the lack of new drugs that can replace the increasingly ineffective set of antibiotics currently available. Worldwide, the pipeline for new antibiotics is limited because of scientific, regulatory and economic barriers. In response to this, multiple governmental and nongovernmental organisation (NGO)-supported initiatives have been implemented at international and national level as an important step to boost the antibiotic research & development (R&D) pipeline.<sup>1</sup>

In the Netherlands, this led to the establishment of the **Netherlands Antibiotic Development Platform (NADP)**, bringing together Dutch academic institutions, medical centers and private organizations working on R&D of antibiotics and alternative therapies spanning the entire spectrum from basic research to clinical Phase IV studies. An initiative that was taken by the Ministry of Public Health, Welfare and Sports together with already existing collaborative networks of public and/or private organizations (see Appendix I) active in antimicrobial research and drug development in The Netherlands.

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<sup>1</sup> Renwick M], Simpkin v, Mossialos E. Targeting innovation in antibiotic drug discovery and development: The need for a One Health – One Europe – One World Framework. Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2016. (Health Policy Series, No. 45.)

# Netherlands Antibiotic Development Platform

The Netherlands Antibiotic Development Platform (NADP) <sup>2</sup> facilitates the collaboration between public and private organisations active in the Life Sciences Health sector with the goal to fill and accelerate the R&D pipeline of new antibiotics and alternative therapies for use in human and animal health care (Figure 1).

To achieve this goal the NADP actively supports:

- Networking between (inter)national public and private organizations active in antimicrobial R&D;
- Identification and initiation of public-private R&D collaborations via alliance management;
- Lead finding and development via NADP support vouchers.

In pursuit of its overall goal, NADP adopts a common Research and Development Agenda (RDA) that defines the long-term focus areas of NADP guiding its efforts and support in the Netherlands. The RDA distinguishes and reflects on the current antibiotic and alternatives research infrastructure of the Life Sciences Health sector in the Netherlands.

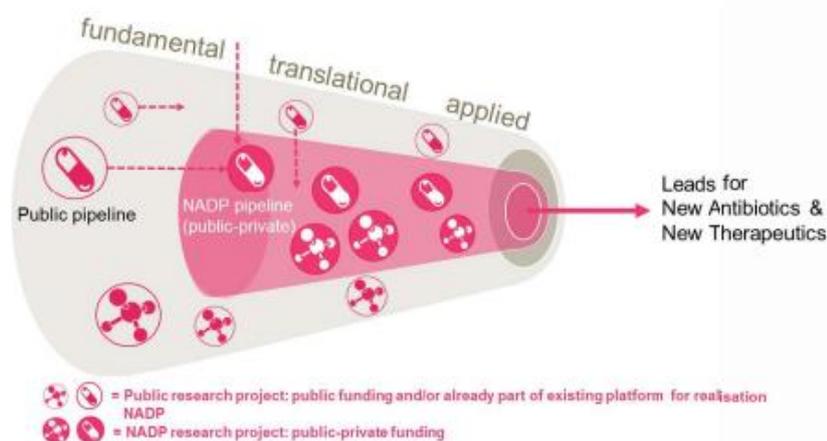


Figure 1. Research of NADP spans from translational and preclinical research leading to applied and clinical studies.

## The Life Sciences Health sector in the Netherlands

The Netherlands is home to a vibrant, concentrated Life Sciences Health cluster with more than 2200 life science and medtech companies and research organisations, all within a 120-mile radius. As such it is the most geographically concentrated region in the world when it comes to creating economic and social value in Life

Sciences and Health. The excellent medical research infrastructure is strongly focused on translational research in different medical fields including infection and immunology of animal and man. Worldwide, the Netherlands ranks 6<sup>th</sup> and 8<sup>th</sup> in life sciences and health citations and patents, respectively.

Within the Netherlands, 10 universities, 8 university medical centers and 3 technological universities are active in R&D of antimicrobial solutions (Figure 2). In nationwide public-private R&D programmes these research organizations cooperate in different niches such as identification and lead optimization of new antibiotics and alternative therapies (NACTAR programme), bacterial vaccine technology development (Bac Vactory programme) and point-of-care diagnostics (ZonMW antimicrobial resistance programme). In

addition, active participation of many of these institutes is seen in European funded R&D programmes. In particular, a prominent role is being played by the Netherlands in the Innovative Medicines Initiative (IMI)-funded program NewDrugs4BadBugs in which amongst others a European clinical infrastructure for anti-infectives efficacy testing is being established (COMBACTE project). Also a number of H2020 programmes are running focused on antibiotic development and production (SynPeptide; Rafts4Biotech).



Figure 2. Universities, university medical centers, and technological universities active in R&D of antimicrobial solutions in the Netherlands.

Abbreviations: Academic Medical Center Amsterdam (AMC), Erasmus Medical Center (EMC), Erasmus University Rotterdam (Ei-JR), Leiden University (LU), Leiden University Medical Center (LUMC), Radboud University Nijmegen (RUN), Radboud University Medical Center Nijmegen (RUMC), Technical University Delft (TUD), Technical University Eindhoven (TUE), University Groningen (RUG), University Medical Center Groningen (UMCG), University Medical Center Maastricht (MUMC+), University Medical Center Utrecht (UMCU), University Twente (UT), Utrecht University (UU), University of Amsterdam (UvA), VU University Amsterdam (VU), VU University Medical Center (VUMC), Wageningen University and Research centre (WI-JR).

## NADP focus areas in research and development

The aim of research within the RDA is to deliver new bioactive compounds and alternatives to antibiotics aimed at curing infectious diseases caused by resistant bacteria. Genome sequencing and the resulting discovery of numerous previously unseen biosynthetic gene clusters and the advent of innovative engineering tools, such as CRISPR-Cas9 and large-scale gene and protein synthesis, have revolutionized science. Also it is becoming increasingly clear that host immune mechanisms are involved in the curative response to antibiotic treatment in case of chronic bacterial infections. Together, these technological and scientific advancements have opened new opportunities to search for new antibiotics and alternative therapies to treat bacterial infections in both humans and animals.

Reflective of the expertise and research excellence in the Netherlands, three focus areas are identified within the NADP that aim to decrease our dependence on last resort antibiotics:

1. New antibiotic molecules;

2. New alternative therapeutics;
3. Clinical infrastructure.

The focus areas enable NADP in its support of collaborations between public and private organisations aimed at finding and accelerating the development of new antibiotics and alternative therapies. The RDA may be incomprehensive but presents the strategic focus points of NADP activities.



Figure 3. NADP focus areas in research and development.

## New antibiotic molecules

There is a need to identify and introduce novel antibiotics that can by-pass the current resistance mechanisms, to alleviate our dependency on the few antibiotics of last resort that are currently available. Antibiotic resistance is dependent on the chemical class and the mechanism of action of the antibiotic, thus new antibiotics must preferably affect novel targets and/or have sufficient structural novelty. Ideally, an antibiotic has multiple targets that are essential to the target cell, possibly including non-protein-based targets. In both cases there is a significantly lower chance of the occurrence of resistance. The overall objective of focus area 'New antibiotic molecules' is to identify and optimize novel antibiotics against Gram-positive and Gram negative pathogenic bacteria, based on novel, preferentially multiple, or non-protein based targets.

Areas of excellence in the Netherlands comprise:

- **Drug discovery:** from the dawn of the antibiotic era to present day, excellence in microbiology has underscored the Dutch contribution to antibiotics research and development. From historic contributions by van Leeuwenhoek, Beyerinck, and Kluver to current dedicated microbiology centers focusing on identification of new antibiotics via isolation of novel molecules from actinomycetes (van Wezel (LU, NIOOKNAW)), the largest fungal collection in the world (den Hertog (KNAW-Hubrecht Institute)), and a large collection of Bacilli with high antimicrobial potential (Kuipers (RUG)). Innovative biotechnology approaches are thereby developed to enable and/or enhance the production of antibiotics and derivatives (van Wezel, Ram (LU), Kuipers (RUG)). Furthermore, an internationally renowned research base in bacterial membrane biogenesis including bacterial protein transport is available and being exploited for the discovery of novel antibiotics (Driessen (RUG), Bitter (VU), Tommassen (UU)). The past decade has also witnessed the continued merging of the fields of biology and chemistry - chemical biology - as related to the pursuit of new antibiotics. Aside from providing new tools for the discovery of novel antibiotics, such as the design of activity-based probes to selectively isolate antibiotics (Overkleeft and van der Stelt (UL), XXX (RUG)), chemical biology approaches can also be applied to understanding the mechanisms of action of novel antibiotics and the mechanisms by which pathogenic bacteria develop antibiotic resistance (UU, RUG,

UMCG). Strengths in chemical biology lie in characterisation and adaptation of antimicrobial compounds (Martin, van Wezel (LU), Kuipers, Minaard (RUG)), and bioinformatics (Medema (WI-JR), XXX (KUN), Abeel (TUD)). Microbial ecology is an important new field in drug discovery, that harnesses natural signals and eliciting conditions to activate biosynthetic gene clusters that are inactive under routine screening conditions (van Wezel (UL), Raaijmakers (NIOO-KNAW)). Variants of naturally occurring antibiotics are engineered via molecular genetics approaches (Kuipers (RUG)). Elucidating antibiotic mechanisms of action and identification of un(der)exploited targets. Application of activity based probes (VU, UvA, UL). Important supporting technologies include organs-on-a-chip in which the Netherlands have a front-running position (Clevers (Hubrecht-KNAW), Hankemeier (UL) and Mummery (LUMC)).

Drug design: the Dutch chemical community is extremely strong and has a reputation for delivering worldclass innovation as evidenced by a recent Nobel prize. Synthetic chemistry (Rutjes (KUN), Martin (LU'), Feringa (RUG), Breukink (LIU)) and innovative concepts (i.e. light-activated antibiotic molecules; Feringa (RUG)) aid in the design of novel structures and libraries and are reflective of excellence in their application to antibiotics. Moreover, synthetic biology approaches have generated large libraries of novel antimicrobial peptides tested by novel high-throughput screening methods, yielding new drug candidates (Kuipers, RUG).

## New alternative therapeutics

A complementary strategy to the development of new antibiotics is the development of alternative modalities, that can either eliminate bacteria without selecting for novel resistance traits, or that modulate the immune response of the host during (or before) infection. Such strategies should be based on mechanisms of action not yet used by existing antibiotics or whose delivery mechanisms are not (or at least less) susceptible to evolutionary resistance pressure, or on better understanding of the innate and humoral immune response to bacterial infections caused by species creating current and future treatment problems because of AMR. The overall objective of focus area 'New alternative therapeutics' is to develop strategies that are targeted towards establishing and/or boosting host immunity as well as reduction of pathogen burden by means of therapies other than broad-spectrum antibiotics.

Areas of excellence in the Netherlands comprise:

- Host-directed therapy: The use of preventive vaccination to boost host immune responses to clear or to accelerate clearance of the bacterial infection is a potent strategy. Research in vaccine technology and vaccine design dates back to 1950 when the Netherlands introduced the National Immunization Program. It has led to strong research communities in infection biology, microbiology, and innate and adaptive immunology. Particularly the understanding and design of immunomodulatory and anti-inflammatory therapy are a primary strength in the Netherlands (van der Poll (AMC), Rooijackers (UMCU), van Strijp (UMCU), Haagsman (UU)). Moreover, the ground-breaking concept of trained immunity foreseen to aid in the design of future vaccine strategies was established by Dutch researchers (Netea (RUMC)). To tackle intracellular infections novel vaccination strategies (mostly in tuberculosis) and host-directed therapy (HDT) are being pioneered in the Netherlands. The latter attempts to reprogram the host immune system by pharmacological and chemical-genetic manipulation. Importantly, HDT-driven manipulation of host signaling pathways may be effective also against drug-resistant bacteria and help to restore host control of infection in metabolically perturbed cells. Promising compounds and host target molecules for HDT against MDR-TB and Salmonella have

been identified by research groups in the Netherlands working in the field of chemical immunology (Ovaa (LU), Neefjes (LUMC), Ottenhoff (LUMC)). The Netherlands have also pioneered in developing microbiomes for host protection and in particular to treat infections with *Clostridium difficile*, using faecal transplants (Kuijper (LUMC)), whereby a faecal transplant bank has been set up (Nederlandse Donor Feces Bank, LUMC).

- Microbe-directed therapies: Antimicrobial host-derived peptides can kill bacteria rapidly. They function as first line of defense in animals and humans. In addition to antimicrobial activity they also have the ability to stimulate the host's immune system and in this way indirectly disable microorganisms. Research groups in the Netherlands are leading experts in the field of unravelling the working mechanisms of antimicrobial host-derived peptides (Nibbering (LUMC), Kuipers (RUG), Haagsman (UU), Zaat (AMC)). In addition, an excellent infrastructure in peptide and protein chemistry and synthesis is available (Drijfhout (LU<sup>1</sup>), Heck (UU), Gros (UU)). Another antimicrobial strategy based on the power of the host's immune system is to combat resistant bacteria via antibody-based therapies. The so-called therapeutic vaccines based on human monoclonal antibodies allows specific targeting of certain bacteria without affecting the host microbiome and thus reducing the risk for antibiotic resistance development. Furthermore, antibodies act immediately and require only basic immune functions that are often retained even in immunocompromised patients. With world-leading academic (Rooijackers (UU), Parren (LUMC)) and industrial (van de Winkel (Genmab)) experts in antibody discovery, antibody biology research, and antibody engineering the Netherlands is at the forefront of this fast-moving field. Finally, development of bacteriophage technologies and research into the clinical benefits of phage therapy show potential as renewed solutions for antimicrobial therapy (Bonten (UMCU), Brouns (TUD), Struijs (EMC)).

## Clinical infrastructure

A major challenge in the antibiotics pipeline is how to bring developed antibiotics and alternative therapeutics into the clinic. The pathway of resistance investigation and from hit to lead is a long one. The time needed for clinical evaluation of promising antibacterial compounds (from phase 1 to phase 3 trials) is generally between 5 and 10 years. The Netherlands includes state-of-the-art 'Clinical Infrastructure' that aims to support the clinical development of antibiotics and alternatives and to improve the efficiency of these difficult (and thus expensive) trials.

Areas of excellence in the Netherlands comprise:

- Clinical trials infrastructure: the European Federation of Pharmaceutical Industrial Associations and IMI have created the New Drugs for Bad Bugs program. An important goal is to create a high-quality clinical and laboratory trial network in Europe to optimize clinical trials with new antimicrobial agents. With a managing entity and coordinator in the Netherlands, the Dutch are leading the development of this clinical trial network COMBACTE (Bonten (UMCU)).
- Infection models: the Netherlands is home to a number of groups developing cutting edge (predictive) methods for how well a given compound might behave as a drug. Such technologies have the power to greatly benefit antibiotics and alternatives research by accelerating the process by which early stage lead compounds become clinical candidates. Importantly, such models also have the potential to reduce the need for animal testing in preclinical evaluation of large numbers of candidate compounds. Particularly exciting technologies being developed and applied in the Netherlands today include organs on a chip

(Clevers (KNAW-Hubrecht), Hankemeier (LU), Mummery (LUMC)), and zebrafish and other infection models (Spaank & Meijer (LU), Bitter (VUmc)).

## Appendix: NADP Partners

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The NADP partners are the Centre for Antimicrobial Research (CARES), the Centre for Sustainable Antimicrobials (CeSAM), Immuno Valley, and the Netherlands Centre for One Health (NCOH).

### Centre for Antimicrobial Research

Centre for Antimicrobial Research (CARES) in Leiden is a Dutch research initiative for antimicrobials research, focusing on the development of novel antibiotics and antimicrobials. The CARES programme aims at delivering novel lead compounds to refill the antibiotic pipelines. An aim in itself is to build a strong collaborative network consisting of universities, university medical centres and companies. Some 15 groups are united within CARES, from both UL and LUMC, with strong focus on actinomycete and fungal microbiology, chemical biology, bioorganic synthesis and design of activity-based probes, host-pathogen interactions, drug development, infectious diseases and immunology. Major pathogens that are targeted include Mycobacterium tuberculosis, Clostridium difficile and Pseudomonas aeruginosa. In 2017 a new profile area on antibiotics was funded by the faculty of sciences (UL), with 6 PhD students working between leading groups in antibiotic research in chemistry, biology and drug research. Furthermore, Leiden has the largest bioscience park of the Netherlands, which offers a strong platform for public-private partnerships.

CARES believes it is vital that the public and private sector jointly take up responsibility to develop new antibiotics and to ensure a continuous supply of novel candidate drugs into clinical trials. CARES focuses on the development of novel compounds and the translational science to bring these new antibiotics to the clinic. Contact person: Prof. Gilles van Wezel

### Centre for Sustainable Antimicrobials

The Centre for Sustainable Antimicrobials (CeSAM) in Groningen comprises creative fundamental research, including advanced facilities for high-throughput (animal) testing and adequate patient-screening. CeSAM's goal lies in interdisciplinary basic and translational research to develop novel antibiotics and therapeutic ('theragnostic') concepts to fight resistant bacterial strains, simultaneously allowing sustainable prevention of resistance development and spreading.

The scientific challenge is to develop novel intelligent and sustainable antimicrobials to combat resistant pathogens, which will be pursued throughout the production pipeline to complete phase I clinical trials. More than 20 chemistry, biology and pharmacy groups are active in the field of antibiotic design, (bio)synthesis, resistance and pharmaceutical characterization, collaborating in various programs, e.g. ALERT (EU-Cofund with 18 PhD students) and Pronkjewail (EU-Cofund, 17 PhD students) both highly focused on antimicrobial development and AMR. The clinical challenge is to develop innovative solutions for personalized on-demand

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4 <https://www.universiteitleiden.nl/cares/>

5 <http://cesam-nnl.com/>

theragnostic strategies based on existing and novel antibiotics to optimize treatment and to prevent both health care-associated infections due to antimicrobial resistance and spreading of resistant strains. Contact Person: Prof. Oscar Kuipers

#### Immuno Valley

Immuno Valley is specialized in matching business and science with the goal to build sustainable partnerships for the research and development of solutions to infectious diseases in humans and animals. In addition, Immuno Valley supports partnerships with specialized services that are designed to maximize collaboration and drive a project forward.

The Immuno Valley team is comprised of professionals with a relevant track record in science and business. The Immuno Valley network comprises multinational pharmaceutical companies, SMEs, academic hospitals, and knowledge institutes active in the field of human and animal health. In the field of infectious diseases, Immuno Valley has previously established the multistakeholder R&D programme on Alternatives to Antibiotics (ALTANT) and also initiated and manages the Bacterial Vaccine Technology Center (Bac Vactory; 6 PhDs and 4

Post-Docs) 8.

Contact Person: Dr. Liana Steeghs

#### Netherlands Centre for One Health

The Netherlands Centre for One Health (NCOH) brings together world-leading academic research institutes in the Netherlands active in various complementary fields of One Health together with other leading parties. Thereby, it forges an open innovation network to take joint responsibility for finding answers to global One Health challenges. The NCOH primarily aims for an integrated approach to tackle the global risk of infectious diseases by considering human, animal, wildlife, and ecosystem health. This virtual science-driven institution focuses its research and increase of knowledge along four major Strategic Research Themes related to infectious diseases: Tackling Antibiotic Resistance (NCOH-AMR), Emerging Infectious Diseases Preparedness (NCOH-EID), Smart and Healthy Farming (NCOH-SHF), and Healthy Wildlife and Ecosystems (NCOH-HWE). The NADP is strategically and organisationally embedded within NCOH-AMR.

The strategic theme NCOH-AMR aims to decrease the morbidity and mortality of antibiotic-resistant bacterial infections in humans through use-inspired, excellent, fundamental, translational, and applied One Health research on antimicrobial resistance. The NCOH-AMR, as other NCOH themes, is organised through so-called Solution Sets. Within NCOH-AMR, the NADP provides a platform for public-private partnerships in the Solution Sets "New Antibiotics" and "New Alternatives". Contact person: Prof. Marc Bonten

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6 <http://www.immunovalley.nl/> 7 <http://www.immunovalley.nl/altant/> 8 <http://www.immunovalley.nl/bac-vactory/> 9 <https://ncoh.nl/>

## 3-B Netherlands research program

### Summary

A lot has been undertaken to tackle antibiotic resistance since the WHO identified this topic as an important threat to public health in 2004. Human health care started to act upon this matter but soon the notion arose that BR is a cross-domain issue. Antibiotic usage in the veterinary sector and the development and spread of antimicrobial resistance in the environment are also part of the problem. Therefore the method requires a One Health approach. 'One Health' is the cross-domain approach to health from the perspective of humans, animals and the environment. These domains are closely related in relation to health.

The Netherlands has made great progress in the fight against antimicrobial resistance. The "search and destroy" policy for dealing with methicillin-resistant *S. aureus* (MRSA) in hospitals has been successful for many years. But more and more we are faced with other types of plasmid-bound resistance that seem difficult to control. An approach that focuses exclusively on care in hospitals is inadequate here.

The broader approach has resulted in a dramatic decline in the use of veterinary antibiotics. Since 2009, a reduction of more than 50% has been achieved. The role of the environment in the system of emergence and spread of AMR is recognized but still raises many questions.

In June 2015, the government letter "Tackling antibiotic resistance" was sent to parliament by the Health Ministry, Ministry of Economic Affairs and I&M. The approach to ABR is described through seven subsectors. Based on this government letter, the Strategic Research Agenda of the JPI AMR and a programming study the following research areas have been identified:

1. Mechanisms for inducing and transmitting antibacterial resistance
2. Appropriate diagnostics
3. Mechanisms and targets for new antibiotics and alternatives to antibiotics
4. Optimising antimicrobial therapy: dosage and use

These themes are in line with the previously mentioned background documents.

Knowledge of theory-driven research is needed to establish the necessary (behavioral) changes in the approach to antibiotic resistance. The scientific background of the theories can be very diverse and depends on the determinants of behavior. Thus, in addition to behavioral sciences, management science or economics for example, also can provide relevant insights that might achieve changes in health care.

The focus of the program is on research whose results within five years after publication can influence the strategy for tackling antibiotic resistance. It is to be expected that applied research can best meet this expectation. Fundamental and translational research is not excluded from the program. Cooperation in international funding instruments is sought, for example by participating in the joint calls of the JPI AMR. The actual development of drugs or vaccines has no place within this program.

## Introduction

In 2004, the World Health Organization (WHO) signalled the emergence of antimicrobial resistance (AMR), along with a steady decline in the discovery of new antimicrobials. The WHO highlighted four control strategies to help stem the tide: (a) surveillance; (b) prevention; (c) research and product development; and (d) international cooperation. AMR is no longer merely emerging but has become an established reality in health care, the open population and in the agricultural and food sectors. In May 2015 the World Health Assembly adopted The Global Action Plan of the World Health Organization (WHO). This plan is based on a One Health approach of AMR and provides a frame for further action. (1)

In 2013, the Joint Programming Initiative on AMR was established. [JPIAMR](#) coordinates national funding and supports collaborative action to fill existing knowledge gaps. Today 22 states are participating in this initiative. The goal is to shape cohesive and coordinated AMR funding and actions that maximise on resources and reduce duplication of research. Mobilising existing and new resources will create a greater critical mass and attract new researchers into the AMR field. A Strategic Research Agenda (SRA), which outlines key [neglected] areas to tackle, guides JPIAMR and focuses research actions.

At the same time, the Netherlands has worked hard to keep AMR at bay – and has been successful in doing so in some areas. The search-and-destroy policies to keep MRSA out of its hospitals has been successful for many years, the reduction of veterinary use of antibiotics has been spectacular and first steps have been taken to gain more insight into the role of the environment in the emergence and spread of AMR. The Dutch government presented its multisectoral approach for combating antibacterial resistance in June 2015. (2)

Prudent use of antibiotics in humans is a main thread of the Dutch approach to antibacterial resistance. Antibiotics can only be obtained with a doctor's prescription. Efforts to further decrease the already prudent use of antibiotics have been successful. Between 2011 and 2014, the defined daily doses of antibiotics sold by pharmacies decreased by 6% (3).

Resistance levels in animals showed an increase in parallel with the increase in antimicrobial use that occurred before 2008, both for individual drugs and multi-drug resistance (MDR). But sales of antibiotics for veterinary use decreased by 58.1% between the years 2009-2014. Parallel to this decrease, the occurrence of resistant bacteria in livestock also decreased (4). Consequently, prudent use as a main thread of the Dutch approach no longer only includes use in humans, but also in livestock.

The presence of resistant organisms in food, animals and the environment is intertwined with human health, and herein lies an important challenge for the Netherlands. To what extent the environment, compared to the clinical and veterinary domains, contributes to human exposure needs to be quantified. (5)

AMR surveillance is the cornerstone for assessing the burden of AMR and for providing the necessary information for action in support of local, national and global strategies. Much work has been done in Europe since the WHO signalled a rise in AMR in combination with a decline of new antimicrobials. For example, the establishment of the European Centre for Disease Prevention and Control (ECDC) provided a major opportunity for an enhanced EU-wide surveillance system. The Dutch National Institute for Public Health and the Environment (RIVM) has played an important part herein and continues to do so. Another major challenge for national and international surveillance networks is the emerging threat of carbapenem resistant bacteria. (6)

Given this emerging threat, there is a great need for new antibiotics. But in the absence of a proper business model, investments by the pharmaceutical industry to develop new antibiotics have fallen sharply. On a European level, the Innovative Medicine Initiative (IMI) is working on this in the New Drugs for Bad Bugs programme (ND4BB). In the UK, a working group chaired by Jim O'Neill published

a report that sets out proposals to address this problem and brings forward the financial reward to new antibiotics that address drug resistance. (7)

While we continue to gain more knowledge into the ways in which antibacterial resistance develops, it is becoming increasingly clear that there is a need for behavioural change towards our approach to infection prevention and antibiotic use. Insight into what drives people and populations to use antibiotics prudently or to take proper actions to prevent the occurrence and spread of infections is necessary. (8,9)

The mechanisms which lead to antimicrobial resistance are biological. However the conditions promoting, or militating against, these biological mechanisms are profoundly social. How our farmers, veterinarians, and regulatory systems manage livestock production for human consumption; how regulatory and fiscal frameworks incentivise or deter antimicrobial development, production and use; how the public and healthcare professionals understand, value and use antimicrobials; the context in which animals and humans interact; the ways in which particular groups of humans are exposed to particular microbial infections; all these are shaped by social, cultural, political and economic forces. Therefore, social science has a key role to play in measuring, modelling, understanding, and where appropriate changing the social environment in relation to antimicrobial resistance. (10,11,12)

To help control antibacterial resistance, the Netherlands organisation for health research and development (ZonMw) opens up the research programme Antibiotic Resistance. With 16 million Euros ZonMw will fund applied and basic/fundamental research as well as implementation projects over a period of six years. The programme's focus is on applied research, but fundamental research that concerns targets for new antibiotics or alternatives will also be funded to a limited extent.

Based on the 'Kamerbrief Antibioticaresistentie' of June 24, 2015, the Strategic Research Agenda of the JPI AMR and a programming study the following research areas have been identified:

1. Mechanisms for inducing and transmitting antibacterial resistance
2. Appropriate diagnostics
3. Mechanisms and targets for new antibiotics and alternatives to antibiotics
4. Optimising antimicrobial therapy: dosage and use

Knowledge from all relevant sciences is considered crucial to achieve the behavioural changes which are necessary to tackle the societal challenge of ABR. Especially theory-driven research is needed to establish the necessary (behavioral) changes. The Dutch Ministry of Health (VWS) commissioned ZonMw to develop the programme Antibiotic Resistance (Appendix 12.1). VWS stressed the importance of international alignment of research and the need for outcomes that support policy decision making in the next five years.

This document describes the Antibiotic Resistance research programme which builds on information from the programming study and technical input from the programme board, as well as on the outcomes from the current Priority Medicines Antimicrobial Resistance programme. First, the logical framework of the programme is outlined (Section 4). The general and specific objectives of the programme are laid down here, jointly with its' expected results and verifiable indicators (Appendix 12.2). Section 5 describes the four research areas within the programme, and gives examples of relevant research questions. Links to other initiatives are summarised in Section 6. Organisational aspects of the programme form the last part of this document, with Communication and implementation (Section 7); Organisation of the programme (Section 8); Monitoring and evaluation (Section 9) and finally Funding structure (Section 10).

## Logical framework

The general aim of the programme is to contribute to the control of antibiotic resistance (ABR), by stimulating research in the field of antibiotics' use and the development and implementation of new medicines or interventions. The scope for antibiotic resistance is in line with the approach that was chosen by the Dutch government. Results of research aim to have considerable impact on strategies for control of antibiotic resistance within five years of publication of those results.

### Specific goals

- To further our understanding of the ABR system in order to prioritize within the overarching approach to ABR control
- To facilitate the development and use of diagnostics in the control of antibiotic resistance
- To help identify mechanisms and targets for new antibacterial drugs or vaccines
- To contribute to optimising antibacterial therapy both in dosage and in use
- 

Besides the specific goals related to the research areas, they also include:

(a) to stimulate knowledge transfer and to create the conditions necessary to implement research results; (b) to foster collaboration between:

- research, policy and practice
- human, animal and environmental health
- the Arts, Sciences and Behavioural Sciences
- public and private partners

A further goal is to foster international collaboration, especially within the JPI AMR. Appendix 12.2 gives an overview of the programme's objectives, expected results and verifiable indicators.

## Research areas

This section describes the research areas within the programme, and gives examples of relevant research questions. Behavioural science and more precisely theory-driven research, is considered to be one of the important research disciplines which could be of added value in all of the research areas. For most changes concerning antibiotic usage, use of diagnostics or other behaviour related to antibiotic resistance a range of factors interact at different levels to determine whether and to what extent change is achieved. For any innovation to be implemented successfully, it is necessary to identify the potential interacting determining factors. In turn, these factors can be described by and derived from different theories that need to be tested for their single or combined influence on change. Therefore behavioural science needs to be more involved in studies concerning antibiotic usage and use of diagnostics. They can be helpful in translating evidence based medicine into desired behaviour. Research aimed at understanding the cultural, contextual and behavioural aspects of antibiotic resistance generates possibilities for interventions to reduce usage of antibiotics, improve or streamline use of diagnostics and to aid in achieving a reduction in the spread of resistant bacteria. In this program, we will, therefore, make an effort to enhance collaboration between biomedical and behavioural research.

## Mechanisms for inducing and transmitting antibacterial resistance

This research area focuses on the epidemiology of ABR. As induction and transmission of ABR is a complex system, further understanding of the processes involved is necessary for intelligent prevention measures. In the current AMR programme, research has been conducted on the transmission of resistant bacteria between animals and humans, the effect of travel and transmission within the hospital setting. For this area, links to (international) surveillance systems are relevant. In the Netherlands, both human and animal ABR is surveyed systematically, as is antimicrobial use (4).

In the history of ABR, veterinary use of antibiotics has played an important role. Veterinary use of antibiotics has been considered one of the main drivers of resistance in the occurrence and spread of VRE, MRSA and ESBL producing bacteria. Following research in all those cases reality turned out to be a bit more complex than that. Occurrence of resistance in the veterinary domain is directly linked to veterinary use of antibiotics. But resistant bacteria in livestock are seldom the same bacteria that cause problems in hospitals. Sequencing of the whole genome of ESBL producing bacteria in humans and livestock has shown that the strains found in humans and the strains found in livestock are not directly related. Shared plasmids, on the other hand, were found. It remains unclear what the reservoir of antibiotic resistant bacteria and ABR genes in livestock means for human health. (13)

In the human part of the One Health approach of research inducing and transmitting ABR the role of antibiotic use in general practice and in nursing homes with regard to occurrence and transmission of ABR is not as well documented as the effects of antibiotic use in hospitals. Also spread of ABR between healthcare facilities needs to be investigated further.

The role of the environment is especially not well understood. As a delta, the Netherlands are more interested in the role which (surface)water plays in the spread of ABR than some other countries. We already know that different types of resistance occur in our surface water. But we don't know what kind of risk this poses for human health. (5)

In short, more insight into pathways and especially the relative risk they are for public health is needed.

Apart from antimicrobials, biocides may also contribute to the increase of ABR. Biocides are disinfectants, antiseptics, preservatives and sterilants used in health care, food production and in consumer products such as tooth paste or cleaning fluids. Some resistance mechanisms are common to both biocides and antimicrobials. Scientific evidence indicates that the use of active molecules in biocidal products may contribute to the increased occurrence of AMR. However, the exact risk formed by the use of biocides is not clear at present.

Relevant research questions in this area include:

- What are the main routes of ABR transmission? Between animals, between animals and humans, between animals and the ecosystem and between the ecosystem and humans? How important are these routes epidemiologically? What is the contribution of biocides?
- To what extent do antibiotic residues in the environment (of both human and animal origin) and resistant bacteria in the environment contribute to the occurrence of resistant bacteria in humans?
- What is the attributive contribution of health care facilities to the spread of ABR within these settings and the open community?
- What is the effect and cost effectiveness of interventions that reduce the spread of ABR?
- What are effective interventions to stimulate hygienic behaviour (in health care facilities and the community), based on a careful assessment of barriers in a well defined situation and a coherent theoretical base?

## Appropriate diagnostics

An important part of prevention of ABR is appropriate diagnostics. Improvements in diagnostic tests can streamline diagnosis and treatment of infectious diseases and support use of antibiotics in a way that reduces the risk of occurrence of ABR. Innovative diagnostic tests are less invasive, give more rapid results and are easier to do (point-of-care tests vs. laboratory tests for example). Appropriate diagnostics can improve initial antimicrobial prescription in cases of infection with ABR pathogens and assist physicians and veterinarians in their decision to prescribe or withhold evidence-based therapy. The right diagnostics improve cost-effectiveness and promote the use of narrow spectrum antibiotics. The challenge in infectious disease control is to develop point-of-care assays that can rapidly detect multiple pathogens, including their resistance patterns.

The needs of a general practitioner differ from those of an intensive care doctor, a doctor in a nursing home or a veterinarian. Diagnostics should meet the needs of the situation and the professionals in the situation, otherwise they will not attribute to a change in prescriptions. Therefore, diagnostics are considered appropriate when they:

- fit within the context of the situation
- give the doctor the right information to act
- fit the urgency of the situation

Multiple techniques for rapid diagnostic testing are expected to become available for clinical use in the coming years. The cost-effectiveness of these tests needs to be carefully determined. The achievement of uniformity of testing, especially internationally, also deserves attention. The focus should be on phenotyping organisms (i.e. determining the characteristics needed for clinical decision making) instead of genotyping them.

Relevant research questions include:

- Can novel approaches for diagnostic testing of ABR microorganisms be developed?
- Can we distinguish between causative organisms quickly, in particular between bacterial and viral infections? Can a test be developed that indicates the severity of an infection?
- What are the predictions for the (cost-) effectiveness of patient admission and discharge screening with a view to future public health threats when patients are transferred from one health care setting to another or go home?
- What are the obstacles that occur when implementing new diagnostics (in human and in veterinary health care) and how can we avoid or overcome them?

## New mechanisms and targets for antibiotics and alternatives to antibiotics

This research area focuses on the **identification of mechanisms and targets for new drugs** in relation to microbial evolution. In this context, the uptake of research outcomes by private partners deserves attention. Fundamental, explorative research can provide a building block for new antimicrobials. A sound approach is necessary: What is it exactly that makes us ill? Can we neutralise this ill-making effect? This research area has direct links to research programmes within the European Innovative Medicine Initiative.

Development of new drugs is a time consuming and expensive process that **requires participation from both academia and partners from industry**. Still also for the results in this research area a considerable influence on the strategy for control of ABR within five years after publication of the results is expected. In the Netherlands, **Immunovalley as well as the Netherlands Centre for One Health (NCOH)** are examples of organisations that build bridges between academia, research institutes, industry, policymakers and NGO's that are needed to work on this subject. **Public funding from the Ministries of Health and Economic Affairs are combined with funding from industry to tackle One Health issues**, including the **development of new antibiotics**. ZonMw will keep abreast of the current initiative of the ministry of Health aimed at narrowing the gap between the discovery of new mechanisms and targets by academia and further development of new antibiotics or alternatives by industry based on those discoveries. Changes for follow up may be bigger for projects within identified structures.

Relevant research questions in this area include:

- **Can new mechanisms and new targets for drugs be identified?**
- **Can alternatives to antimicrobial use be identified?**
- **Which passive or active immune therapies can be used?**
- **What are the underlying mechanisms that determine the evolutionary behaviour of ABR in humans and animals? This includes molecular epidemiology and physiological studies.**
- **How can the gap between the discovery of promising targets and mechanisms in academia and the development of new antibiotics or alternatives by industry be bridged?**

## Optimising antimicrobial therapy: dosage and use

More prudent use of antibiotics in people and animals is the first recommendation in the JPI AMR's Strategic Research Agenda. Research in this area contributes to the quality, safety and efficacy of antimicrobial use in different settings. The most favourable antimicrobial therapy has an optimal prescription, dosage (including timing) and use. **Optimum dosage and reductions in the length of antimicrobial treatment may alleviate the selection pressure for antimicrobial resistance**. Optimum timing is also important in the prevention of infections. This is the case in human health care (e.g. in surgery) but also in veterinary practice, where population size and husbandry practices hamper curing infection at population level by just treating individuals. **Behaviour of doctors and patients, veterinarians and farmers plays a role when an optimal treatment as described in a guideline or protocol is, or is not, put into practice.**

This research area focuses on the epidemiology of ABR, the role of antimicrobial use in the introduction, spread and transmission of ABR and **ways to use or combine antibiotics to limit the risk of resistance development**. Prescribing antibiotics is unique in the sense that not only the individual patient has to be taken into account but that prudent use is also necessary from a public health perspective. In the Netherlands, the SWAB and the NHG set up guidelines for prudent use of antibiotics in hospitals and general practice. For veterinary use, the KNMvD working group on veterinary use of antibiotics is doing the same.

Dutch usage of antimicrobials in humans is still sparse and targeted, and remains amongst the lowest in Europe. Veterinary use of antibiotics in production animals has decreased over 50% in the last few years. Is there still room for improvement? Some settings (e.g. home care and possibly primary care) and some patient groups (children, the elderly) are not well represented in research. Moreover, guidelines on the use of antibiotics for specific settings such as nursing homes and facilities for handicapped persons are scarce.

Nursing homes are of particular interest as they seem to form a reservoir of ABR and find it difficult to improve infection prevention. They might even play a role in the spread (or continuous re-introduction) of ABR in different health care settings. In addition, new challenges lie in informal routes of acquiring antibiotics, such as over the counter purchases brought home by migrants and travellers, or purchases through the internet.

In order to change behavior concerning use of antibiotics, knowledge that is developed by biomedical research needs to be combined with knowledge gained by behavioral science. To be efficient, those disciplines need to come together. Studying behavior and determinants of the target audience is needed to ensure that people display the desired behavior. The target audience can, of course, also be veterinarians, farmers and pet owners.

Research questions in this area include:

- Which interventions combine an optimum therapeutic effect with a minimal selection for resistance?
- What are the determinants of prescribers' and patients' appropriate antimicrobial use (e.g. required action, specific patient group)? Which determinants can be influenced, and how can we do this in practice in a (cost)effective way?
- Is under-dosage of antimicrobial therapy related to ABR?
- How can antibiotics be combined in a way that the risk of inducing transmittable resistance in the patient and his/her surroundings is limited?
- What are main determinants of high antibiotic use on farms and can we influence them while preserving animal welfare?

## Links to other initiatives

This chapter gives a brief overview of organisations that conduct activities or policy initiatives in the field of AMR control.

### Dutch (funding) organisations

#### ZonMw

Besides the ABR research programme, also the programme on Infectious Disease Control and the 'Good Usage of Drugs' programme cover topics related to ABR. Research questions that consider general infection prevention are covered by the Infectious Disease Control program. This ABR program focuses on transmission of ABR, appropriate diagnostics and appropriate use of antibiotics. Within the 'Good Usage of Drugs' clinical trials related to antibiotics are funded. The ABR program does not exclude this kind of research. Applicants can submit their project in both programs. When projects that are qualified and relevant cannot be funded because the budget is insufficient, the programs can refer applicants. The efforts of ZonMw in the area of research related to antibiotic resistance is outlined on the [ZonMw webpage](#).

#### VWS

In addition to funding the ZonMw ABR programme, the ministry of Health is also exploring ways to align science, research and (pharmaceutical) industries in the Netherlands in order to create optimal conditions for the development of new antibiotics. Within this collaboration funds may become available.

#### NWO

AMR is a specific topic in the topsector Agri&Food. Research in this area will be funded in the two year programme in 2016 and 2017. In other NWO programmes with a broader scope research related to antibiotic resistance is also funded.

#### WOTRO

WOTRO Science for Global Development is the division within NWO which supports scientific research on development issues, in particular poverty alleviation and sustainable development. WOTRO is funded by NWO and the Dutch Ministry of Foreign Affairs (BZ). WOTRO has identified four research themes based on internationally recognized research agendas related to the United Nations Millennium Development Goals.

One of these WOTRO themes – Global Health and Health Systems – is directed at research and knowledge transfer to contribute to achieving 3 Millennium Development Goals: (a) combat HIV/AIDS, malaria and other diseases; (b) reduce child mortality; and (c) improve maternal health. In line with this theme, WOTRO wishes to stimulate excellent research aimed at contributing to reducing the burden of infectious diseases and antimicrobial resistance. The ABR programme will investigate the possibilities for collaboration with WOTRO.

#### STW

The basic strategy of STW is to bring together scientists and technical users around excellent scientific and technical research. Projects in different research areas can relate to antibiotic resistance. Bac-Vactory is a STW funded consortium aiming to develop new vaccines against bacteria based on a One Health approach.

## EZ

The Dutch Ministry of Economic Affairs (EZ) will facilitate the realization of the pacts sealed between animal husbandry organisations in the various production sectors, by co-funding the development and distribution of knowledge and development of monitoring instruments and systems. EZ intends to extend the funding of the present research programme ALTANT. Thus, the market introduction of promising alternatives to antimicrobials can be facilitated. Through the 1Health4Food research programme, based on public-private cooperation, EZ is funding research that contributes to further reduction of antibiotic use in production animals.

## FIGON

The Netherlands Federation for Innovative Drug Research (FIGON) is an integrative platform for innovative drug research in the Netherlands. It enhances existing initiatives and signals new developments. ZonMw actively supports the activities of FIGON.

## RIVM Cib

RIVM's Centre for Infectious Disease Control (Cib) is involved in the AMR surveillance and MRSA research. In addition, the Cib is setting up a surveillance system that will enable real time monitoring of health care AMR.

Cib is also involved in public campaigns on the correct use of antibiotics. It will examine the prevalence of the use of antibiotics in nursing homes, in collaboration with SWAB. Results of the program will be shared with the Cib for implementation purposes.

## Professional societies

Professional societies that are active in scientific research in the field of AMR include:

- VIZ (Society for Infectious Diseases)
- NVMM (Dutch Society for Medical Microbiology)
- NVZA (Dutch Society of Hospital Pharmacists)
- NHG (Dutch Society of Family Physicians)

## International programmes and initiatives

In this section the main international initiatives are described.

### ECDC

The European Centre for Disease Control (ECDC) acknowledges AMR as one of the major threats related to infectious disease. It deploys many activities in relation to AMR such as the European Antibiotic Awareness Day. In addition, the ECDC supports European (surveillance) networks, including:

- ESAC (European Surveillance of Antimicrobial Consumption) ([www.esac.ua.ac.be/](http://www.esac.ua.ac.be/)). The core of ESAC's work is to maintain a database on antibiotic use in Europe. In addition, ESAC studies antibiotic usage in different settings such as hospitals or ambulatory care.
- EARSS (European Antimicrobial Resistance Surveillance System) ([www.rivm.nl/earss](http://www.rivm.nl/earss))
- ARMed (Antibiotic Resistance Surveillance and Control in the Mediterranean Region) ([www.slh.gov.mt/armed](http://www.slh.gov.mt/armed))
- Med-Vet-Net is a network of excellence that integrates the medical, veterinary and food sciences. Part of the work of Med-Vet-Net is an investigation of AMR in bacterial strains from many sources along the food chain

### DG SANCO

Projects related to AMR initiated by DG Sanco include:

- SCORE (Strategic Council on Resistance in Europe)
- Antibiotic Strategies (ABS) International ([www.abs-international.eu](http://www.abs-international.eu))
- Burden of Resistance and Disease in European Nations ([www.eu-burden.info](http://www.eu-burden.info))

## **DG Research**

The most recent AMR projects funded under Horizon 2020 are listed in Section 12.5 in the Appendix.

## **JPI AMR**

The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) joins forces across nations to fight AMR through effective collaborative actions in areas of unmet needs. A shared common research agenda enhances multi-disciplinary collaboration and ensures that knowledge gaps are quickly identified and filled.

## **CDC**

The United States' Centres for Disease Control and Prevention (CDC) deploys a range of AMR-related activities. To name a few: a national AMR surveillance system, a national campaign to prevent AMR in health care settings and several public campaigns (e.g. educational activities to promote appropriate use of antibiotics agents in animals).

## **WHO**

In May 2015, WHO launched the Global action plan on antimicrobial resistance. This plan sets out five strategic objectives:

- To improve awareness and understanding of antimicrobial resistance
- To strengthen knowledge through surveillance and research
- To reduce the incidence of infection
- To optimize the use of antimicrobial agents
- To develop the economic case for sustainable investment that take account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

The WHO presents a mapping of AMR related initiatives.

## Communication and implementation

As stated earlier, three of the specific goals of the ABR research programme are (a) to stimulate knowledge transfer (b) to create the conditions necessary to implement research results and (c) to foster collaboration between research, policy and practice, animal and human health, alpha, beta and gamma sciences and public and private partners. These specific goals are a prerequisite to achieve the programme's more general aim: to contribute to the control of antibacterial resistance, by stimulating research in the field of antibiotics' use and the development of new medicines or interventions. Attention to communication and implementation is crucial to these three specific goals, both at project level and at programme level. This section outlines the most important aspects of communication and implementation within the AMR research programme.

### Starting points

The specific goals and expected results, with regard to implementation and communication, have been outlined in Section 4 and in 12.3 in the Appendix. The following starting points have been formulated to achieve the specific goals and the expected results:

#### Data sharing and data re-use

Data, which also includes strains and collections, that has been acquired using public funds should be made available to others. In the case of results that could be patented, a longer time period can be agreed upon before these are made available. However, data and other useful deliverables remain public property and should be made available as soon as possible. Data management is a standard part of ZonMw criteria and described on the [website](#). In the ABR programme ZonMw aims to stimulate the use of existing networks to enhance sharing and re-using of data and collections.

#### Communication with the sponsor

The programme has a special relationship with its sponsor VWS. Communication takes place on a regular basis and concerns process, bottlenecks and (provisional) results.

#### Definition of the network

An efficient communication and implementation policy requires a definition of the network in which the programme is rolled out. Relevant questions are: who is the sponsor? Who is the executive? Who is the policy maker? Who is the owner of this problem? How are communication channels organised? What are the gaps? Which fields have strong working relationships and in which fields is further investment in collaboration needed? What is the position of the programme within the network? What parties are involved in harmonisation? Who is in charge? Who will take over?

#### Active network responsibility

The programme committee and the secretariat have an active responsibility in the network. At programme level, they are responsible for maintaining contact, making appointments, and channelling information and input from the field and policy makers towards ongoing projects.

#### Collaboration incentive

The programme aims at active incentives for collaboration between research parties. Project proposals will be judged on collaboration efforts. If necessary, ZonMw can suggest potential partners to get acquainted, exchange information and harmonise their policy. ZonMw can use its communication tools to this extent and link up to existing channels of communication.

#### Successful implementation

In the midterm progress report, the project manager has to respond to questions about knowledge transfer and implementation of the possible results of the project. This plan will be evaluated jointly with the progress report. At the end of the project, an evaluation will be conducted that examines the extent to which all intentions in the plan have been put to practice. In the case of a gap between plan and practice, activities that bridge this gap will be identified. After the finalisation of the project, ZonMw can follow up the implementation of the project for up to 4 years. In addition, ZonMw can support implementation activities.

### **Agreement of (end) users**

Each project proposal describes how the research question and the project's aim have been established with the assistance of practice and policy makers. Where possible, the proposal describes what agreements have been made with future users of the project's results. Anticipation of end results usage is a key element on which the project proposal is judged

### **Transfer of programme results to educational programmes**

ZonMw selects educational institutions for the delegation of knowledge from the programmes and defines concrete agreements for the use of programme results in educational programmes.

## **Methodology**

The afore mentioned starting points result in a methodology, with relevance to communication at project level as well as at programme level:

- Periodical meetings – project manager meeting, stakeholders meetings, expert meetings
- Progress reports and annual reports for the sponsors
- Implementation of lessons learnt considering data sharing and data re-use
- Incorporation of project information in the ZonMw database
- Distribution of news items and programme results through the an e-mail newsletter, Pre-Post, Mediator, scientific journals and the regional and national press
- Information through a sub site of the ZonMw website
- Progress reports and final reports

## Organisation of the programme

This section discusses how the programme is to be organised and the procedures that will guarantee the quality, independence and relevance (to society and otherwise) of the research results.

### The role of ZonMw

ZonMw works to strengthen health and health care. It does so by fostering and financing research, development and implementation. ZonMw has an independent position – between research, policy and practice. Within its programmatic working method, the programme committee plays a central role.

### The programme committee

The board of ZonMw has appointed a programme committee (12.6 in the Appendix). Members have been appointed in their personal capacity. Criteria in the selection process were:

- Knowledge of, experience with and affinity for the field of ABR
- Knowledge of and affinity for research
- Diversity of its members (e.g. background, working place, gender)

Observers from VWS and EZ will be invited to committee meetings. The committee is responsible for formulating and executing the programme. Specific tasks of the committee are:

- To formulate the ABR research programme and supplemental documents;
- To contribute to locating additional funding;
- To prioritise and advise on the awarding of proposals;
- To monitor and evaluate the programme and make adjustments where needed;
- To contribute to communication efforts on the research programme Antibiotic Resistance, in order to enhance coherence and collaboration;
- To contribute to the dissemination of results of the programme and to create the conditions necessary to bring these results into practice;
- To foster and monitor the usage of knowledge gained.

ZonMw strongly feels that decision making should be as objective as possible and exercised by careful and transparent procedures. To do so, conflicts of interest – or even a hint thereof – are banned. To this purpose, ZonMw makes use of a code of conduct which is available in the public domain

([http://www.zonmw.nl/fileadmin/cm/subsidiewijzer/documenten/Code\\_Belangenvstrengeling\\_ZonMw\\_engels.pdf](http://www.zonmw.nl/fileadmin/cm/subsidiewijzer/documenten/Code_Belangenvstrengeling_ZonMw_engels.pdf)). It is the responsibility of the bureau of ZonMw to apply this code correctly. In addition, the chair of the committee and the programme officer with the authority to withhold specific information from individual committee members. This concerns committee members involved –directly or indirectly – in proposals, where the specified information would give them an unfair advantage over noncommittee members.

### Working method

The research programme ABR intends to organise three calls for project ideas; one in 2016, one in 2017 and one in 2018. A detailed timeline is included in Section 12.7 in the Appendix. The first call covers all research areas, with emphasis on the research areas 'Mechanisms for inducing and transmitting antibacterial resistance' and 'Appropriate diagnostics'. For all research areas, social sciences are considered to be of particular value. It is the responsibility of the applicant to check if his or her specific research question has not yet been answered by existing research. The program committee will at least check if the submitted proposal does not demonstrate too much similarity with research conducted within H2020 projects, joint calls of the JPI AMR, or previous projects from the AMR program or the current ABR program. The discovery of new points of action for drugs or vaccines, is clearly a part of this research programme. The development of new drugs or vaccines has no place in the programme.

Overall, awarded projects will encompass all research areas and strike a balance between:

- Applied versus fundamental research
- Research by (larger) consortia vs. individual (or smaller) groups
- Short-term vs. long-term research
- Research with a national perspective vs. an international perspective, linked to research areas in the EU seventh Framework programme, Horizon 2020 and to the research agenda of the JPI AMR

The number of awarded projects and the number of projects awarded per research area will be coordinated by the programme committee, and depends upon the available budget.

Within ZonMw, the ABR programme will align its working method with other ZonMw programmes if necessary. In addition, the ABR programme will seek - and continue already existing - collaboration with external parties, such as WOTRO, EZ and others.

## **Procedures**

ZonMw has established procedures to evaluate proposals for all its programmes. A description of ZonMw's procedures is available in the brochure 'Procedures voor ZonMw-programma's' (in Dutch) at [www.zonmw.nl](http://www.zonmw.nl). Alternatively order by mail ([info@zonmw.nl](mailto:info@zonmw.nl)) or by phone: +31 (0)70 3495133.

The ABR programme committee will use the overall procedures and working methods of the previous AMR programme. The committee will set out more detailed procedures following the submission of proposals for the first call. At that time the exact weighing of the quality and relevance of project proposals will also be determined.

## Abbreviations

ABRES	Interdepartmental Platform Antibiotic Resistance
ALTANT	Alternatives for the problem of antimicrobial resistance in animal husbandry
AMR	Antimicrobial Resistance
BZ	Dutch Ministry of Foreign Affairs
CEO	Chief Executive Officer
CDC	Centre for Disease Control
CIb	Centre for Infectious Disease Control Netherlands
CSBR	Centres for Systems Biology Research
CTMM	Center for Translational Molecular Medicine
CVI	Central Veterinary Institute
DGV	Dutch Institute for Rational Use of Medicine
ECDC	European Centre for Disease Control
EARSS	European Antimicrobial Resistance Surveillance System
EASAC	European Academies Science Advisory Council
ESAC	European Surveillance of Antimicrobial Consumption
ESBL	Extended spectrum beta lactamase
EZ	Dutch Ministry of Economic Affairs
FIGON	Netherlands Federation for Innovative Drug Research
GD	Animal Health Service Deventer
GGD	Institutes for Public Health Services
GR	Health Council of the Netherlands
KNAW	Royal Netherlands Academy of Arts and Sciences
KNCV	Dutch Tuberculosis Foundation
KNMvD	Royal Dutch Society of Veterinarians
LNV	Ministry of Agriculture, Nature and Food Quality
MARAN	Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands
MRSA	Methicillin-resistant S.aureus
NHG	Dutch Society of Family Physicians
NIVEL	Netherlands Institute for Health Services Research
NVWA	Food and Consumer Product Safety Authority
NWO	Netherlands Organisation for Scientific Research
RGO	Advisory Council on Health Research
RIVM	National Institute for Public Health and the Environment
SCORE	Strategic Council on Resistance in Europe
SWAB	Dutch Working Party on Antibiotic Policy
TI Pharma	Top Institute Pharma
VANTURES	Veterinary Antibiotic Usage and Resistance Surveillance Working Group
VWS	Ministry of Health, Welfare and Sport
WHO	World Health Organization
WIP	Dutch Working Party on Infection Prevention
WOTRO	Science Division NWO which supports scientific research on development issues
ZonMw	The Netherlands organisation for health research and development

## Programme objectives, results and indicators

Matrix of programme's objectives, expected results and verifiable indicators

General objective		
To contribute to the control of antibacterial resistance by facilitating and stimulating scientific research. Results of funded research aim to have considerable impact on strategies for control of antibiotic resistance within five years of publication of those results.		
Specific objectives	Expected results	Verifiable indicators
To further our understanding of the ABR system in order to prioritize within the overarching approach to ABR control	Proposals have been awarded and research projects have started	Number of completed projects
To facilitate the development and use of diagnostics in the control of antibiotic resistance	<p>Diagnostics that support the control of antimicrobial resistance have been developed</p> <p>Collaboration with private partners has been established to further develop the insights gained</p>	<p>Number of completed projects</p> <p>Number of projects with collaboration with private partners</p>
To help identify mechanisms and targets for new antibacterial drugs or vaccines	Awarded proposals are aligned with other activities for antibiotic or vaccine development in the Netherlands	Number of projects in which follow up of the results is arranged
To contribute to optimising antimicrobial therapy both in dosage and in use	<p>Proposals have been awarded</p> <p>Research into patients' compliance and physicians' adherence to guidelines has started</p>	<p>Number of completed projects</p> <p>Number of guidelines and/or protocols that have been adapted or developed</p> <p>Number of guidelines and/or protocols that have been evaluated</p>
To help develop interventions for the prevention and control of ABR	Proposals including behavioural science have been awarded.	<p>Number of projects in which behavioural science plays a role</p> <p>Number of implemented projects in which behavioural science plays a role</p>

Specific objectives	Expected results	Verifiable indicators
<b>To stimulate knowledge transfer and to create the conditions necessary to implement research results</b>	<p>Projects´ results have been disseminated in the scientific community, in the field of infectious disease control and to end users when applicable</p> <p>Project leaders have made concrete contributions to the transfer of knowledge</p> <p>Data sharing and data re-use is implemented with using existing infrastructures</p>	<p>Number of guidelines and/or protocols that have been adapted or developed</p> <p>Number of articles published in journals</p> <p>Number of projects that disseminated results in another way e.g. through the popular media</p> <p>Number of projects with results incorporated in training programmes e.g. of health staff</p> <p>Number of projects that have re-used data</p> <p>Number of projects that made their data available for re-use</p>
<b>To foster collaboration between (a) research, policy and practice; (b) animal and human health; (c) the Arts, Sciences and Behavioural Sciences and (d) public and private partners. In addition, to foster international collaboration especially within the framework of the JPIAMR.</b>	<p>Collaboration has been established within projects or between projects</p> <p>Partnerships have been formed or strengthened</p> <p>Strategic alliances have been build</p>	<p>Number of projects in which collaboration was established</p> <p>Number of projects with collaboration between the animal and human health sector</p> <p>Number of public private partnerships that has been formed or strengthened</p> <p>Number of projects with international collaboration</p> <p>Number of contacts with partners (programme committee)</p>

## Appendix 4 - Norway research priorities

This document contains documented Norwegian national priorities related to research and innovation for antimicrobial resistance (AMR) and healthcare-associated infections (HCAI). These priorities have been extracted from the current National Strategy against Antibiotic Resistance 2015-2020<sup>2</sup>. Only priorities related to research and innovation have been extracted. The distinction between research and other activities (like surveillance) is not always clear. For this mapping, only those activities that appear to require time-limited research or innovation activities in order to answer knowledge gaps or produce needed technologies have been included. The Norwegian National Action Plan against Antibiotic Resistance in the Health Sector 2015-2020<sup>3</sup> does not contain research and innovation goals. Norway is currently developing a list of knowledge gaps related to HCAI which is expected in June 2018.

The following priorities have been extracted verbatim from the English-language version of the National Strategy.

Section	Priority
§1	Overarching goal: Improved knowledge of what drives the development and spread of antibiotic resistance
§1	Sector-specific goals – health: Studies will be carried out on the burden of disease as a consequence of antibiotic resistance, as a consequence of possibly too little antibiotic use, and the effect of infection control measures.
§1	Sector-specific goals – climate and environment: Studies will be initiated to explore the effect in nature of other drivers of resistance, including disinfectants, biocides and heavy metals.
§2	The issue of resistance is complex and calls for a better scientific knowledge base so that we can have a comprehensive view of the human and natural factors that limit or encourage the development of resistance. For instance, little is understood about where and how resistance arises and is spread among bacteria in various ecological niches, or whether combinations of resistance factors are maintained or change over time.
§2	There is a lack of knowledge of the spread of resistance genes through food and what risks this creates for consumers... There is also a lack of knowledge of which fact can best reduce continued carriage of resistant bacteria among infected individuals.
§2	The government will assess whether new infection control measures are warranted in the overall food chain.
§2	The government will assess the need for changing recommendations concerning kitchen hygiene and risk communications on food handling in the context of emergence of resistant bacteria.
§2	More needs to be known about the importance of sanitation and the management of fertilizer to prevent the spread of resistance, either presently seen or emerging. This is as true on the human side as on the animal, where the consequences of the use of manure as fertilizer and its runoff into the environment for the development of resistance are not well understood. Research is needed concerning how best to spread fertilizer without spreading resistance.

<sup>2</sup> <https://www.regjeringen.no/en/dokumenter/national-strategy-against-antibiotic-resistance/id2424598/>

<sup>3</sup> <https://www.regjeringen.no/contentassets/915655269bc04a47928fce917e4b25f5/handlingsplan-antibiotikaresistens.pdf>

§2	It will be useful to research the impact on antibiotic resistance of the systematic use of food additives, including other drugs aside from those classified as antibiotics – for example, zinc and copper which are added to swine and poultry feed, as well as coccidiostats added to poultry feed.
§2	Other chemicals (including disinfectants, biocides and heavy metals) can lead to emergence of resistance. To establish optimal strategies, it is important to understand which chemicals are especially strongly associated with increased resistance. We also need to establish a program of basic research to understand the biological mechanisms underlying these effects.
§2	The government will initiate studies to explore the effects of resistance-promoters other than antibiotics, including disinfectants, biocides and heavy metals, in the natural environment.
§2	The government will assure that studies are carried out on the burden of disease resulting from antibiotic resistance and associated economic costs.
§2	The government will improve the monitoring and analysis of incidences of resistant bacteria, both in clinical isolates (from infections), capacity of the healthy portion of the population to act as carriers and, in particular, incidences of infection associated with the health services.
§2	The government will ensure that studies are carried out of the effectiveness of general infection prevention and control measures.
§2	The government will support efforts to develop new and better vaccines.
§2	The government will help to develop better diagnostic methods for infectious diseases and alternative treatment strategies in the areas of both human and animal health, through participation in international research collaborations.
§2	The government will implement measures to cleanse environments of concentrations of resistant bacteria, if new knowledge and cost/benefit evaluations indicate this would be expedient.
§2	The government will consider increasing contributions to research that can lead to new or better antibiotics and diagnostic methods, including through the JPI-AMR.

## Appendix 5 - Slovenia research priorities

The document contains documented Slovenian national priorities related to research and innovation for antimicrobial resistance (AMR) and healthcare-associated infections (HAIs). We have identified these priorities from the National Action Plan (NAP)/National Strategy against Antibiotic (AB) Resistance 2015–2020 (document in preparation).

Current AMR, HAI and AB monitoring in Slovenia: National AMR surveillance in humans and participation in TESSy (European Antimicrobial Resistance Surveillance Network – EARS-Net/Food- and Waterborne Diseases and Zoonoses Network – FWD-Net), AB (ESAC-Net) and HAI (Healthcare-Associated Infections Surveillance Network – HAI-Net) surveillance/monitoring. National Institute for Public Health (NIJZ) coordinates EARS-Net and FWD-Net (data obtained from Institute for Microbiology and Immunology – IMI/National Laboratory of Health, Environment, and Food – NLZOH). University Clinical Centre Ljubljana/NIJZ coordinate ESAC-Net. NIJZ coordinates HAI-Net conducting PPSs on HAIs and AB use based on European centre for disease prevention and control (ECDC) protocol.

NAP for Preventing and Managing HAIs in Slovenia and NAP for Control of Resistance against ABs are both in preparation. Slovenian NAP against AMR and HAIs in the Health Sector 2015–2020 is being currently developed within the Intersectoral Coordinating Mechanism (ICM) for antimicrobial/AB stewardship (ABS) at the Ministerial level – the ICM/ Ministry of Health (MoH), where national multidisciplinary/multisectoral coordinating group facilitates/coordinates development of AMR NAP among the key negotiating partners (NIJZ, NLZOH, IMI, and MoH). ICM for ABS prepared the proposals for NAP, which is currently at the final stage of the coordination with the Directorate of Public Health at the MoH. After the national reconciliation, NAP for AMR is going into the public debate, and then to the Government for final approval. The plan is to decrease the total resistance rate and HAI prevalence and to decrease the total AB use in ambulatory care for at least 25% and for 10% in hospital care. NAP goal is to reduce diseases burden in animals and improve the production results.

Three pillars of the NSs are: i) surveillance/monitoring of AB consumption and measures for prescribing optimization, ii) surveillance/monitoring of AMR, iii) surveillance/monitoring of HAIs, together with: iv) raising awareness among health workers/IPC leaders/health facility leaders/MoHs/patients/patient advocacy groups, v) CME/training vi) research and innovation and vii) international collaboration; decision on planned activities, organization and management, and indicators measured in individual pillars are yet to be decided by the ICM/MoH multisectoral agreement ratified by the MoH.

NAP for AMR and HAIs that is currently in preparation is based on the “One Health” approach as human and veterinary sector are included (environment domain is excluded). NAP is being prepared under the competent authority/MoH and the representatives from the Ministry of Agriculture are collaborating members of the Intersectoral mechanisms.

The following research priorities have been identified from the Slovenian NAP in preparation:

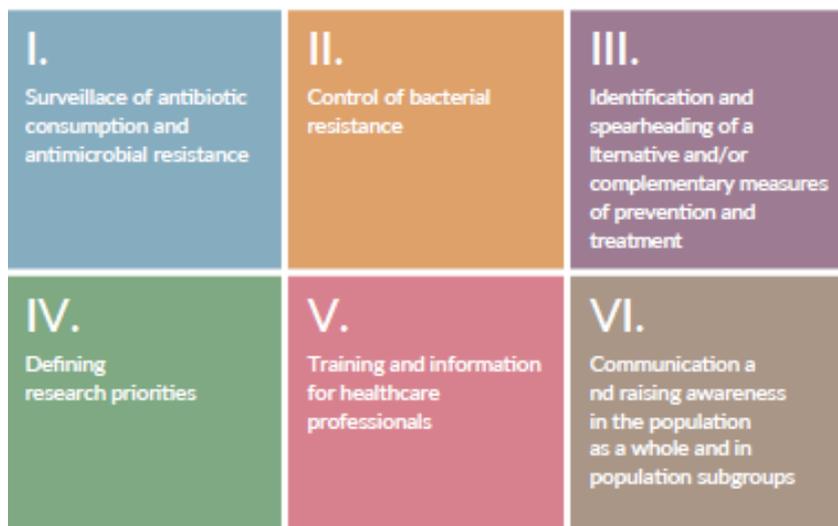
- Studies will be carried out on the overall burden of disease in humans because of inappropriate AB prescribing or as a consequence of possibly limited use of microbiologic diagnostics, which would allow for timely de-escalation to a narrower spectrum agent in ambulatory care and in hospital care.

- Studies will be carried out on the reduction of the overall burden of disease in animals as a consequence of lower consumption of ABs in animals, based on decreased needs for use of ABs in animals by implementing good breeding practices, maintaining the required hygiene conditions and implementing other measures for the prevention of infections and transmission of infections, by implementing the biosafety measures at holdings, and thus decreasing the need for use of ABs in animals.
- Studies will be initiated on the effectiveness of general infection prevention and control measures on microbial infections and their transmission (effectiveness of the introduction of flock/herd vaccines)

## Appendix 6 - Spain research priorities

These priorities have been extracted from the Strategic Action Plan to reduce the risk of selection and dissemination of antibiotic resistance, coordinated by the Spanish Agency of Medicines and Medical Devices<sup>4</sup>.

The plan is structured around six strategic lines common to both human and veterinary health, which are set out schematically in the following figure:



The strategic line IV is Defining of priorities in research. It is divided into two measures:

### **MEASURE IV.1.- Develop and promote a common strategy in research**

Transfer the importance of financing projects linked to this plan and give priority to their funding. Promote and support the search for new molecules so as to increase the therapeutic arsenal and provide new alternatives. This search and its application in veterinary medicine will be developed bearing in mind the importance and impact of said molecules in human medicine.

#### **Human and animal health actions:**

IV.1.1. Promote research to improve knowledge of the mechanisms of AMR.

IV.1.2. Encourage research to improve knowledge of the causes and consequences of the appearance and dissemination of AMR as well as the measures for its control and improvement in antibiotic use.

IV.1.3. Promote the development of value added antibiotics against those already on the market.

IV.1.4. Promote research of alternatives to antibiotics in the field of immunity.

IV.1.5. Support research of new antibiotics that are restricted for use in veterinary medicine but not critical for human medicine.

<sup>4</sup> <http://www.resistenciaantibioticos.es/es/publicaciones/spanish-action-plan-antimicrobial-resistance>

- IV.1.6. Promote the development of new methods of detection and characterisation of AMR.
- IV.1.7. Study incentive mechanisms for research projects based on the identified needs.
- IV.1.8. Encourage research of new indications and ways of using known antibiotics.

#### **MEASURE IV.2.- Development of epidemiological and socioeconomic research**

A better understanding is required of the socioeconomic and medical context of antibiotic consumption and the development of AMR and its consequences. Not only is it a medical problem but also one that is social and the election of actions may depend on the comparative assessment of the principal strategies for prevention of the appearance or propagation of AMR.

##### **a) human health actions:**

- IV.2.1. Improve knowledge of the critical aspects that lead to inappropriate use of antibiotics in outpatients and obtain conclusions to propose interventions aimed at the rational use of antibiotics.
- IV.2.2. Evaluate the consequences of antibiotic resistance (mortality/ morbidity, years of healthy life lost), as well as the associated costs (from the point of view of the community, social protection bodies and healthcare centres) and the effects of the strategies of prevention and care of infections due to resistant bacteria.
- IV.2.3. Improve knowledge of the quality of therapeutic care in primary and hospital care (quality factors, propagation factors and application of recommendations, assessment of the impact of public decisions on the control of bacterial resistance).

##### **b) animal health actions:**

- IV.2.4. Improve understanding of the critical factors that lead to a high consumption of antibiotics on farms.

## Appendix 7 - United-Kingdom research priorities

This document contains the research ambitions and priorities for antimicrobial resistance (AMR) and healthcare-associated infections (HCAI), based on the current National Strategy against Antimicrobial Resistance (AMR) 2013-2018<sup>5</sup>. The strategy highlights how "relevant Research Councils, industry and third sector should work together to establish a range of new mechanisms, including the use of consortia, to facilitate greater collaborative working". The Research Councils, other funders and academics collaborate to ensure that research needs to continue to be identified as the evidence base evolves and that key priorities are funded, improve the knowledge and understanding of AMR by:

- responding to the 'NIHR call for AMR research' 26 in autumn 2013, with proposals to increase the evidence base in the areas of better prevention, improved surveillance and monitoring and diagnosis as well as the more effective use of existing antibiotics, improved education and training and the development of new antimicrobial therapies and better treatment strategies
- developing AMR research capability in the following areas: novel approaches to surveillance and better integration of information infrastructure to determine the spread of infectious including point-of-care diagnostics to avoid inappropriate treatment and reduce antibiotic misuse, innovation in antimicrobial development and the provision of evidence for novel molecules to be developed into drugs
- exploring the possibility of developing a 'drug resistance index' to communicate gaps in antibiotic effectiveness to non-experts and help aggregate data on resistance to various drugs to assess trends in drug resistance over time and across locations, evaluating the effectiveness and consequences of strategies to increase heterogeneity in antimicrobial prescribing and the impact of rapid diagnostics as these are introduced.
- developing new treatments for bacterial infections, from rigorous identification of new targets through to new approaches to treatment
- contributing to European Union work to map what research is ongoing across Europe to help identify areas for further work
- developing coalitions between academia and biopharmaceutical companies
- working to improve diagnostic technology for infection and develop rapid diagnostics, which will allow movement away from broad-spectrum treatments to more tailored treatment approaches

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<sup>5</sup> <https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018>

- utilising the 'Innovative Medicines Initiative' (IMI),<sup>33</sup> a joint undertaking between the European Union and the European pharmaceutical industry, which may facilitate more efficient discovery and development of better and safer medicines for patients
- developing new lead structures for drug discovery projects in the public and private sectors supporting international initiatives to combat AMR, including developing drugs, diagnostics, innovative alternative therapies, combination therapy and optimal dosing regimens across human and veterinary sectors
- promoting the development and uptake of genomic technologies relating to AMR, particularly as the price of genomic testing falls and its power increases

**Other examples of UK research funding include:**

The AMR Funders Forum, led by the Medical Research Council, which brings together major research funders and government departments to promote joint action to understand and tackle AMR through a 'One-Health' approach. The forum has been a platform to identify gaps and opportunities in our understanding of AMR and has established unprecedented levels of research collaboration together with increased investment. Commitments made in 2016 include:

The AMR cross research council initiative: £8m commitment by the research councils, led by MRC, to support research that will accelerate therapeutics and diagnostics development (this includes small molecules, alternative therapies as well as diagnostics), £6.5m commitment by the research councils, led by NERC, to understand AMR and its interaction with the real world (the outdoor environment and the microbiome), £13m commitment by the research councils, led by ESRC, in partnership with DH, DEFRA and VMD to understand AMR and behavioural change within and beyond the health care setting and a £2m commitment by the research councils, led by AHRC, looking at AMR in the indoor and built environment. The Newton Fund: £4.5m by the research councils under the Newton Fund, led by MRC, with matched funding from the National Natural Science Foundation of China (NSFC) to support six new research partnerships that will foster collaboration across borders and between diverse disciplines to help tackle AMR.

The National Institute for Health Research (NIHR) which operates a number of research funding schemes in the area of AMR in order to improve patient and public outcomes and NHS services. As part of the NIHR's activities in this area, the NIHR AMR Reference Group was established to provide direction and guidance on important areas for future research which would be achievable within a reasonable timeframe and have maximum impact on patient and public outcomes. The NIHR AMR Reference Group identified the following key priorities to guide future research and the NIHR would particularly welcome applications on, although not limited to, research in these areas:

**Theme 1:** Reducing the Need for Antibiotic Use - Improving infection prevention and control practices in both healthcare and community settings

**Theme 2:** Supporting and Promoting the Responsible Use of Antibiotics - Optimising prescribing practice in primary and secondary care

**Theme 3:** Diagnostics and New Technologies - New treatments and technologies which contribute to a reduction in antimicrobial resistance

As the new UK AMR Strategy is currently being finalised, new research priorities will emerge 'recommendations' for further research will be raised, based on up-to-date literature reviews and knowledge of what evidence is needed for policy or practice.

## Appendix 8: Case study\_Identifying AMR knowledge gaps and research priorities

### Norway

The European Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI) aims to contribute to a coordinated European response in regards to prioritizing and assisting in the implementation of research and innovation expected to help achieve public health-related AMR and HCAI goals and objectives. The first task of work package 9 (WP9) is defined as:

*Task 9.1: Work with Member States to ensure that national processes for research and innovation priority-setting are grounded in a broad One Health approach and that both Member State research priorities and knowledge gaps are addressed in the development of the update of the JPIAMR SRA*

The first step of this task is to gather best practices of national efforts to identify knowledge gaps and research priorities for antimicrobial resistance (AMR). Norway was suggested as a useful case study due to active participation in JPIAMR and since it has published both a National Strategy against Antibiotic Resistance 2015-2020<sup>6</sup> and a National Action Plan against Antibiotic Resistance in Healthcare Services (2016)<sup>7</sup>.

#### Identifying knowledge gaps and research priorities

In March 2013, four ministries of the Norwegian government (Health and Care Services, Fisheries, Agriculture and Food, and Climate and Environment) established a multi-disciplinary expert group, with a mandate to write a report summarizing existing AMR evidence, identifying knowledge gaps, and recommending priorities and potential measures by November 2013. This deadline was extended to summarize the evidence regarding LA-MRSA in swine populations, a particular concern at the time. This resulted in a 77-page report delivered in August 2014<sup>8</sup>.

The findings of this report were used to develop Norway's National Strategy which includes R&D goals by focus area. An early version of the knowledge gap report was also shared with JPIAMR for their processes in developing the Strategic Research Agenda (SRA), which was published in December 2013.

In 2017, the Norwegian Research Council commissioned a report to map Norwegian research and development (R&D) activities, as a part of ongoing monitoring

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<sup>6</sup> <https://www.regjeringen.no/en/dokumenter/national-strategy-against-antibiotic-resistance/id2424598/>

<sup>7</sup> <https://www.regjeringen.no/contentassets/915655269bc04a47928fce917e4b25f5/handlingsplan-antibiotikaresistens.pdf>

<sup>8</sup> <https://www.fhi.no/publ/2014/antibiotikaresistens--kunnskapshull/>

activities of the National Strategy. The report was published in June 2018<sup>9</sup> and found that Norwegian researchers used about € 57 million (NOK 537 million) in 2017 for AMR-related R&D. This includes € 1.1 million (NOK 10 million) of financing from the European Commission. Whereas this report comprehensively details Norwegian AMR R&D efforts, it does not compare ongoing R&D efforts to the identified knowledge gaps identified in 2014.

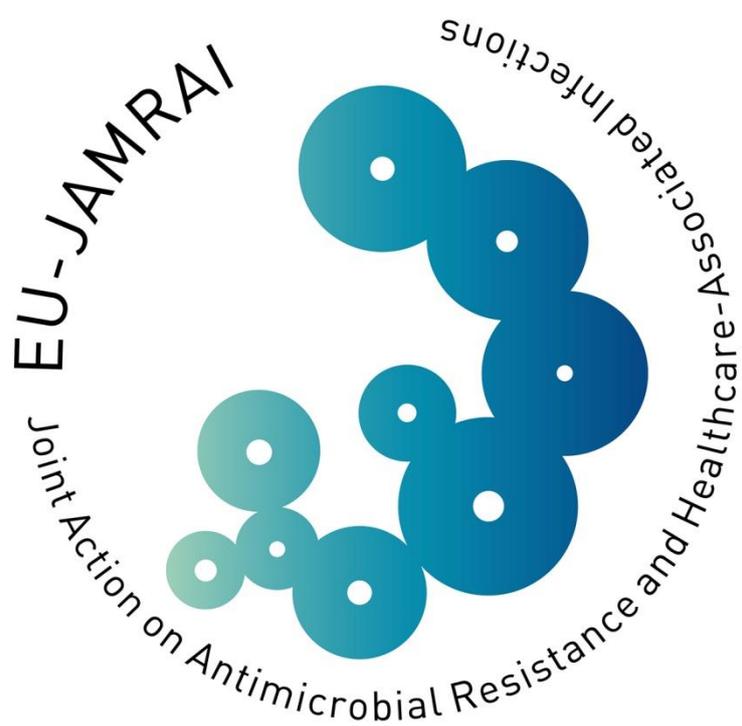
Norway partially relies on JPIAMR to maintain an awareness of where the current knowledge gaps exist, particularly through the work of the Scientific Advisory Board. Norway has an independent expert on this board, but he acts independently representing a thematic area (surveillance) and does not represent Norway. The Norwegian Management Board members see the 2018 SRA update as a minor update and have not consulted other agencies or stakeholders.

## Conclusion

Norway made a significant one-off investment to identify AMR knowledge gaps and research priorities, but there is no plan that this should be a regular process. This will likely be revisited in 2020 when the National Strategy expires. Norway partially relies on JPIAMR and its experts to ensure that knowledge gaps are researched and new gaps identified. There is no formal process to continuously identify AMR-related knowledge gaps of national consequence. Yet Norway is a small, informal country where experts can readily approach national policymakers with ongoing inputs and/or concerns.

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<sup>9</sup> <https://www.nifu.no/publications/1588410/>



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