Antibiotic Resistance

Research Programme

7 december 2015

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1. Samenvatting

Sinds de WHO in 2004 antimicrobiële resistentie heeft benoemd als een belangrijke bedreiging voor de volksgezondheid is veel gebeurd in de aanpak van dit vraagstuk. Waar de humane gezondheidszorg het thema als eerste heeft aangepakt, is het besef ontstaan dat dit vraagstuk domeinoverstijgend van aard is. Ook antibioticagebruik in de veterinaire sector en de ontwikkeling en verspreiding van antimicrobiële resistentie in het milieu vormen onderdeel van het probleem. De aanpak vraagt daarom om een One Health benadering. 'One Health' is de integrale benadering van gezondheid vanuit het perspectief van mens, dier en milieu. Deze domeinen zijn nauw verbonden in relatie tot gezondheid.

In Nederland zijn in de strijd tegen antimicrobiële resistentie al grote stappen gemaakt. Het 'search and destroy' beleid voor de aanpak van methicilline resistente S. aureus (MRSA) in ziekenhuizen is al jaren succesvol. Meer en meer worden we echter geconfronteerd met andere, plasmide-gebonden typen resistentie die lastig te bestrijden lijken. Een aanpak die zich uitsluitend richt op de zorg in ziekenhuizen is hier niet toereikend.

De bredere aanpak heeft onder meer geresulteerd in een dramatische daling in het veterinair antibioticagebruik. Sinds 2009 is een reductie van meer dan 50% gerealiseerd. De rol van het milieu in het systeem van ontstaan en verspreiden van AMR is erkend en roept nog veel vragen op.

In juni 2015 is de kamerbrief 'Aanpak antibioticaresistentie' verzonden aan de Tweede Kamer door VWS, EZ en I&M. Hierin is de aanpak beschreven via zeven deelsectoren. Samen met de Strategische Onderzoeksagenda van het JPI AMR en de kennisagenda AMR die door ZonMw is opgesteld vormt dit de basis voor het onderzoeksprogramma Antibacterial Resistance. Dit onderzoeksprogramma steunt onderzoek binnen de volgende onderzoeksthema's:

- Mechanismen voor het ontstaan en de verspreiding van antibacteriële resistentie
- Geschikte diagnostiek
- Mechanismen en doelen voor nieuwe antibiotica en alternatieven voor antibiotica
- Optimaliseren van antimicrobiële therapie: dosering en gebruik

Deze thema's zijn in lijn met de eerder genoemde achtergronddocumenten.

Kennis uit theoriegestuurd onderzoek is nodig om de noodzakelijke (gedrags)veranderingen tot stand te brengen in de aanpak van antibiotica resistentie. De wetenschappelijke achtergrond van de theorieën kan zeer divers zijn en hangt af van de determinanten van het gedrag. Zo kunnen naast gedragswetenschappen ook organisatiekunde of economie bijvoorbeeld relevante inzichten leveren die veranderingen in zorg kunnen realiseren.

De nadruk binnen het programma ligt op onderzoek waarvan de uitkomsten binnen vijf jaar na publicatie invloed kunnen uitoefenen op de strategie voor de aanpak van antibioticaresistentie. Het ligt in de lijn der verwachting dat toegepast onderzoek hieraan het meeste tegemoet komt. Fundamenteel en translationeel onderzoek is echter niet uitgesloten van het programma. Hiervoor wordt nadrukkelijk aansluiting gezocht met internationale financieringsbronnen, bijvoorbeeld door de bijdrage aan de joint calls van het JPI AMR. De daadwerkelijke ontwikkeling van medicijnen of vaccins heeft geen plaats binnen dit programma.

2. 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 succesful 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 lettre, 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.

3. 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 initiatieve. 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 extend.

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).

4. 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
- To help develop theory based change interventions for the prevention and control of ABR

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 an 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.

5. 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.

5.1 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 practise 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?3
- 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?

5.2 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?

5.3 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?

5.4 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?

6. Links to other initiatives

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

6.1 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 tot 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 recognised 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 realisation 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)

6.2 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/). 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)
- ARMed (Antibiotic Resistance Surveillance and Control in the Mediterranean Region) (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)
- Burden of Resistance and Disease in European Nations (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.

7. 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, alfa, bèta 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.

7.1 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.

7.2 Methodology

The affore 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

8. 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.

8.1 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.

8.2 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_Belangenverstrengeling_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 non-committee members.

8.3 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 to 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.

8.4 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. Alternatively order by mail (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.

8.4.1 General procedures concerning proposals

The committee will decide to stimulate bottom-up and/or top-down research, dependent on the principal research theme and the financing institution. There are 7 steps in the evaluation of proposals:

- Call for project ideas: ZonMw places a call on its website, in Mediator and professional media if needed. The call requests interested parties to submit project ideas within 8 weeks.
- Evaluation of project ideas: mainly based on relevance and broadly on research quality
- Call for proposals: ZonMw will invite researchers of selected project ideas to submit a detailed proposal
- External review and comment round: each detailed proposal will be refereed by two or more independent reviewers. Reviewers are selected from different fields of expertise and may differ in their opinions. Applicants can respond in writing to the anonymous reviews
- Quality evaluation: the programme committee will make a final evaluation on the quality of submitted proposals, based on the anonymous reviews and the written response of the applicant
- Evaluation of relevance and prioritization: the programme committee makes a final judgement on the relevance of the proposed research and prioritises proposals based on both relevance and quality. For the method of prioritising please see example 2 in the brochure Procedures.
- The reward or rejection of submitted proposals: the committee advises the board of ZonMw on the reward or rejection of submitted proposals. On behalf of the board ZonMw´s CEO will inform applicants of the board's final decision

8.4.2 Criteria to evaluate relevance

The relevance criteria mentioned here below are intended to inform submitters as well as the programme committee. In addition, submission forms are designed so as to encourage submitters to explicitly demonstrate the relevance of the project by using the relevance criteria.

Contribution of the submitted project to aims and goals of the programme
Does the project fit within the general and specific scope of the programme, and does it contribute to its aims and the aim of the One Health approach?

Innovative
Is this an innovative project? Does the project generate new insights?

Public and or scientific interest
Does the project meet public needs? Does the project address knowledge gaps? Can results of the project be used for

Access to Data
ZonMw encourages optimal use of data. In the project idea or full proposal the applicant describes the possibilities to make use of existing data or collections. When a new data set or collection of strains or samples is being build, the the applicant shall indicate how to make them accessible, preferably by using existing infrastructures.

Costs and benefits
Does the project strike a balance between effort, input and means on the one hand and (expected) results and impact on the other hand?

Participation
ZonMw is committed to participation: involving stakeholders in projects. Stakeholders are not just groups who are professionally engaged in research, or health care, but also (potential) service users and citizens. By 'involving' we mean consulting or collaboration in the project.

Attention to gender, culture, age, the patient's perspective and specific risk groups including livestock
ZonMw considers attention to these aspects crucial and includes them in to the evaluation of a project's relevance. Proposals have to define why they do or do not give attention to these aspects with referees to support.
ICT and ehealth: ZonMw gives ICT and eHealth (where possible and appropriate) attention in the programmes and grant calls. The way may vary per project. A distinction is made between research, development and implementation projects. Does your project focus on e-health or is ICT otherwise involved in the project? Then look at the page ICT and e-health on the website of ZonMw. Here you can read what criteria must be considered.

Attention to dissemination of results and the implementation of a project's results
Attention to the further use of a project's output is part of any research project. For projects in which development is an important part, attention to the further use of a project's output will be part of the evaluation of a project's relevance and quality. The criteria used to evaluate the dissemination and implementation of project results may differ along project type. Aspects for evaluation can be :

- Is there an adequate strategy for the dissemination and implementation of results?
- Are stake-holders user-groups well defined?
- Are such groups actively involved in the project?
- What specific activities are scheduled?
- Are the right people and/or groups involved in these activities?

8.4.3 Criteria to evaluate quality

ZonMw has laid down general criteria to evaluate the quality of submitted projects:

Objective, problem definition and/or assignment
Original projects with scope and a clear objective are what is looked for. An objective must be clear and specific. Research objectives need a specific and verifiable research question. In projects concerned with development and implementation the assignment needs to be clearly defined, practical and consistent with a broader objective. Scope is of importance: how important is the subject, what is the theoretical or empirical evidence presented in support of the problem definition/assignment and does the project add value to existing knowledge or practice? A proposed project may not be a repetition of any (running) project

Strategy
The strategy is clear and suffices to carry out the project. It describes the methods and analyses supported by a theoretical or empirical framework. If there is a target group, the strategy defines how gender, culture, age, and specific risk groups are reflected in the project. In addition, the degree of collaboration with intermediate and/or ultimate target groups (the patient/client perspective) is outlined here.

Access to data
ZonMw encourages optimal use of data. In project idea or full proposal the applicant describes the possibilities to make use of existing data files and biobanks. When it is necessery to collect new data, strains or samples datamanagement procedures are described. When a new data set is set up, the applicant shall indicate how access to them afterwards is regulated. What applies for data also applies body material or bacterial strains. Use of existing infrastructures is preferred.

Project group
Factors associated with a successful project group can include relevant experience, familiarity with the area in question and prior activities and projects. Publications, guidelines and interventions and the number and nature of grants received as well as (international) contacts with peers and target groups may reflect a group's success. Notwithstanding, promising new talent stands a good chance to secure funding of their proposal.

Feasibility
It should be likely that a projects objective or assignment can be achieved with the proposed strategy and with the available and/or requested means, staff and facilities. A timeline must be realistic. Projects need to pay attention to any factors that may impede or facilitate the process.

Development and implementation projects: attention to the dissemination and implementation of results

8.4.4 Specific criteria Antibiotic Resistance

Some criteria are specific to the programme and will assist with prioritising proposals:

Projects that are embedded in wider (regional) networks with the following key elements:
- Collaboration between municipal health services, health care providers, universities and/or knowledge centres
- Coherence at a national level
- Interaction between research, education and practice
- Research led by real life problems
- Output (products and services) based on science and with a use in practice

Projects in all research areas are funded during the course of the program. For all research areas behaviourall sciences are considered to be of particular value.

Attention to collaboration. Collaboration within projects is considered valuable. Given the One Health character of antibiotic resistance, collaboration between partners in the human, veterinary and environmental domains is considered valuable. Collaboration between different scientific areas (e.g. biomedical and social science, chemistry and biology) is stimulated. The concrete nature of the collaboration and its sustainability will be part of the evaluation of a project.

Attention to European and international research agendas and to international collaboration.
Is international collaboration relevant for the proposed project or not? Are similar projects undertaken abroad and can researchers link up or learn lessons from these projects? In particular, collaboration with partners in ´endemic´ countries in e.g. Eastern and Southern Europe may be of relevance. It is evident that project proposals should not overlap with any existing research project. Project proposals may however link with existing projects that receive international funding. It is a prerequisite that such a proposal is a logical next step, originating from, but very much independent from, the existing research project.

9. Monitoring and evaluation

The progress of the programme is monitored by the programme committee.

Projects´ progress
The progress of awarded research projects is monitored by the programme committee and based on midterm progress reports and final reports submitted by the project managers. The programme committee evaluates whether the project is on schedule, based on the original project proposal. In addition, they assess whether the project needs amendments or adjustments. The committee focuses specifically on how researchers promote the implementation of the research results. After the completion of a project, ZonMw actively follows the project for 1 up to 4 years on the progress of the dissemination of results and the implementation of the project's results.

Progress of the programme
The programme committee keeps sponsors and potential users posted on the progress of the programme by means of an annual progress report. Primary focus of the report is to describe how programme activities have contributed to programme targets. The expected results and verifiable indicators that were outlined in Sections 4 and 12.3 in the Appendix will be used in this context. These reports give the programme committee and sponsors all the relevant information to adjust the programme, if necessary.

Evaluation of the programme
The programme runs from 2016 until 2022 and can be expanded depending on potential sponsors. The programme committee evaluates the programme once during the term of the programme and once after the conclusion of the term. Evaluation is based on granting criteria and performance indicators decided upon, together with the sponsors, prior to the start of the programme. The evaluation focuses on programme priorities, working methods and procedures, results, time schedule and budget. The results of the evaluation are described in a programme report that is presented to the sponsors.

10. Funding structure

Budget Projects	€ 13,090,000
Communication and implementation	€ 568,940
General costs (committee costs included)	€ 238,000
Cost of current issues and alternatives	€ 750,000
Programme costs	€ 1,353,060

Total	€ 16,000,000

Budget projects		
First round	50%	€ 4,645,000
Second round	30%	€ 2,787,000
Third round	20%	€ 1,858,000
Top down		€ 800,000

Total		€ 10,090,000

Budget projects JPI AMR	
2016	€ 1,000,000
2017	€ 1,000,000
2018	€ 1,000,000

Total	€ 3,000,000

Participation in Joint Actions is based on relevance for the Dutch situation. Budget that is left over in European calls because of the funding system can be transferred to the national calls.

Yearly a budget of €150.000 is reserved for answering current (policy) issues or funding experiments e.g. activities for realising data sharing and data re-use. Budget that is left over can be transferred to the national calls.

11. 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

12. Appendices

12.1 Letter VWS concerning the Antibiotic Resistance Programme

Ministerie van Volksgezondheid,
Welzijn en Sport

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2015/21909/zonmw

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Directie Publieke Gezondheid
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Kenmerk
862876-143423-PG

Correspondentie uitsluitend richten aan het retouradres met vermelding van de datum en het kenmerk van deze brief.

Datum 30 OKT. 2015
Betreft Opdracht tot het opstellen van een vervolgprogramma Antibioticaresistentie

Geacht bestuur,

In de afgelopen maanden heeft ZonMw op verzoek van VWS een kennisagenda Antibioticaresistentie opgesteld. Hierin heeft een brede inventarisatie plaatsgevonden van de behoefte aan kennis op het gebied van antibioticaresistentie bij betrokken veldpartijen. Ik wil u verzoeken om als vervolgstap te komen tot een voorstel voor een vervolgprogramma Antibioticaresistentie voor de komende vijf jaar. VWS en ZonMw streven er naar om de start van het programma te laten samenvallen met het moment van de grote Europese Conferentie van Ministers van Zorg en Landbouw op 9 en10 februari 2016. Daarbij verzoek ik u met de volgende aandachtspunten rekening te houden.

Het programma dient de pijlers van de strategische onderzoeksagenda van het JPI AMR als uitgangspunt te nemen, evenals de kamerbrief Antibioticaresistentie van 24 juni 2015. Dit betekent inhoudelijk dat de One Health aanpak, zoals toegelicht in de brief van 24 juni, de grondslag is voor de reikwijdte en invulling van het programma. Verder ligt voor dit programma de nadruk op toegepast, kortdurend onderzoek, en veel minder op langdurig fundamenteel onderzoek.

Het onderwerp antibioticaresistentie staat op dit moment in de belangstelling. Er zijn al vele initiatieven in ontwikkeling en uitvoering op dit thema. Daarom verzoek ik u rekening te houden met andere (onderzoeks-)activiteiten op het onderwerp antibioticaresistentie, binnen bestaande programma's bij ZonMw maar ook daarbuiten, om overlap te voorkomen. In het kader van de Meerjarenagenda Zorg, onderdeel van de aanpak Antibioticaresistentie, wordt bijvoorbeeld door betrokken veldpartijen gewerkt aan de vormgeving van regionale netwerken, landelijk dekkende surveillance en de voorstellen voor een toekomstbestendige inhoud, organisatie en financiering van richtlijnen op het gebied van infectiepreventie, naleven van hygiëneregels en zorgvuldig voorschrijven van antibiotica.

We verzoeken u een programma te ontwikkelen waarin heldere prioriteiten worden gekozen, waarin bij beoordeling van de ingediende voorstellen aandacht is voor de uitvoerbaarheid en implementatie.

Tevens vragen we u oog te hebben voor de meest efficiënte en effectieve inzet van de beschikbare financiële middelen. Hierbij kan gedacht worden aan mogelijkheden van cofinanciering door andere overheden of via Europese onderzoeksprogramma's en fondsen.

Ik verzoek u bij het programmavoorstel een begroting en liquiditeitsprognose op te nemen. Voor het programma is een bedrag van maximaal € 16.000.000 beschikbaar. De jaarlijkse verdeling van de middelen is als volgt: 2016 € 1.100.000, 2017 € 1.900.000, 2018 € 2.600.000, 2019 € 3.300.000, 2020 € 3.300.000, 2021 € 2.600.000 en 2022 € 1.200.000.

Ik wens u succes met het opstellen van dit programma en zie uw voorstel graag binnen de afgesproken termijn tegemoet. Ik stel voor dat tussentijds een concept versie ter bespreking wordt voorgelegd aan het programmateam Antibioticaresistentie. U kunt hiervoor mw. Damiët Onderstal, programmasecretaris, als contactpersoon beschouwen.

Hoogachtend,

de directeur-generaal Volksgezondheid,

b/a

mw. drs. A. Berg

Directie Publieke Gezondheid
programma antibioticaresistentie

Kenmerk
862876-143423-PG

12.2 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 n 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	Diagnostics that support the control of antimicrobial resistance have been developed Collaboration with private partners has been established to further develop the insights gained	Number of completed projects Number of projects with collaboration with private partners
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	Proposals have been awarded Research in to patients´ compliance and physicians´ adherence to guidelines has started	Number of completed projects Number of guidelines and/or protocols that have been adapted or developed Number of guidelines and/or protocols that have been evaluated
To help develop interventions for the prevention and control of ABR	Proposals including behavioural science have been awarded.	Number of projects in which behavioural science plays a role Number of implemented projects in which behavioural science plays a role

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

12.3 Recent antimicrobial resistance projects funded under Horizon 2020

Listed here are the most recent AMR projects funded under Horizon 2020. More information is available at: http://cordis.europa.eu/home_en.html.

- AntibioDx: AntibioDx: A groundbreaking in vitro diagnostic device with a billion-dollar sales potential
- ACTICAPS: Actiwhey based microencapsulation solution for sustainable food manufacturing
- resistance evolution - Bacterial evolution of hypersensitivity and resistance against antimicrobial peptides
- PROTOCOL: New processing technology for colistmethate sodium, leading to improved and cost-effective formulations for pharmaceutical and veterinary markets
- PHOCCS: Photon Cross Correlation Spectroscopy
- ACT against AMR: Abyssomicin C Truncated derivatives against Antimicrobial Resistance
- BARREL Barrel Assemblies of Membrane Active Artificial Foldamers
- PneumoCompetence: Unravelling the mechanisms of competence induction by antibiotic stress in Streptococcus pneumoniae
- MathModExp: The Evolution of Competition and Cooperation: how polymorphisms in microbial populations optimise virulence and mediate drug resistance
- INTEGRATE: Interdisciplinary Training Network for Validation of Gram-Negative Antibacterial Targets

12.4 Programme committee members

Chair	**Organisation**
Dr. J.M.M. de Gouw	GGD Hollands Midden, vestiging Leiden
Co-chair	
Prof. dr. J.W.M. van der Meer	
Members	
Dr. M.J. Boeree	UMC St. Radboud
Prof. dr. A W. (Alexander) Friedrich	UMC Groningen
Dr. B.W.K. Ganter	VU
Prof. Dr. I.C. Gyssens	UMC St. Radboud
Prof. J.A.P. Heesterbeek	Faculteit Diergeneeskunde Utrecht
Dr. M.E.J.L. Hulscher	UMC St. Radboud
Dr. M. Kretzschmar (ma/do rivm)	RIVM
Dr. M. Kretzschmar (di, woe, vrij)	Universitair Medisch Centrum Utrecht
Prof. Dr. O.P. Kuipers	Rijksuniversiteit Groningen
Prof. Dr. J.M. Prins	Academisch Medisch Centrum
Prof. dr. R.C. Pool	UVA
Dr. M.F. Schim van der Loeff	GGD Amsterdam
Dr. A. Timen	RIVM / LCI
Prof. dr. C.M.J.E. Vandenbroucke-Grauls	VU Medisch Centrum
Prof. dr. Th. J.M. Verheij	Universitair Medisch Centrum Utrecht
Prof. dr. J.A. Wagenaar	Universiteit Utrecht
Prof. B.A.M. van der Zeijst PhD	Leiden University Centre
Waarnemers	
G.W. Dekker	VWS
N. Antonisse	NWO/WOTRO
F. Zeilmaker	EZ

12.5 Timeline

9 February 2016	First call opens
9 April 2016	Deadline submission Project ideas
second week May 2016	Meeting Programme Committee
first week June 2016	Committee recommendations to submitters
1 September 2016	Deadline submission Proposals
Second week November 2016	Decision, awarding/rejection letters
Second week May 2017	Deadline for start of project
Early 2017	Second call opens
Early 2018	Third call opens

Information on ZonMw's general time schedule is available on http://www.zonmw.nl/nl/subsidies/procedure/

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