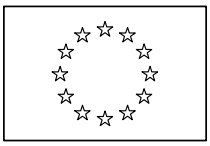

EUROPEAN COMMISSION

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**COMMISSION STAFF WORKING PAPER**

**Accompanying document to the**
**COMMISSION RECOMMENDATION ON THE RESEARCH JOINT PROGRAMMING INITIATIVE 'THE MICROBIAL CHALLENGE – AN EMERGING THREAT TO HUMAN HEALTH'**

{C(2011) 7660 final}

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# I. Executive Summary

The Commission proposes a more strategic cooperation between European Union (EU) Member States on research and development to address major societal challenges under the umbrella of the European Research Area (ERA). One way of unifying research programmes and activities with a transnational perspective on national, regional and European levels is a new 'joint programming' approach. Joint Programming Initiatives (JPIs) involve Member States engaging on a variable-geometry basis in defining, developing and implementing strategic research agendas (SRAs). "The Microbial Challenge – An Emerging Threat to Human Health" has been proposed as one such JPI, with a focus on the rapid increase of antimicrobial resistance (AMR) and the threat this poses to human health.[1]

The microbial challenge, due to increasing resistance to antimicrobial drugs, represents one of the major emerging threats to human health in the 21st century[2]. The increased use of antimicrobials – predominantly but not exclusively, antibiotics – has been accompanied by the development of AMR, i.e. the phenomenon that microorganisms causing infections develop resistance to currently available drugs. Resistance rates to a single antibiotic exceed 40-50% in some European countries[3], and resistance to multiple antibiotics is a common and increasing problem. In healthcare settings, AMR notably represents a threat of particular concern. Infections resistant to antimicrobial drugs are among the most common cause of healthcare associated infections, i.e. infections occurring after exposure in a hospital or a healthcare service unit.

In the EU, about 4 million patients are estimated to acquire a healthcare-associated infection each year[4]. The annual additional burden posed by resistance, focusing only on a limited group of healthcare-associated bacterial infections, is at least 2.5 million hospital days, 400,000 infections, 25,000 deaths and economic losses on the order of €1.5 billion due to extra healthcare costs and productivity losses[5]. Infectious diseases caused by resistant bacteria result in additional healthcare costs and indirect costs, such as sick-leave and output lost due to premature death. The indirect costs to European countries are likely to be several-fold higher[6].

With the introduction of antimicrobial drugs, society acquired the tools to combat many life-threatening infections caused by microorganisms, such as bacteria, viruses, fungi and parasites. The discovery of antibiotics in the mid-twentieth century revolutionised the management and treatment of bacterial infections. Infectious diseases that had previously been fatal became curable. Antibiotics have saved the lives and eased the suffering of millions of people. Today, antimicrobials are crucial in treating bacterial infections, especially in high-risk patients, e.g. those in intensive care, and those receiving organ transplants, cancer chemotherapy and prenatal care. However, these gains are in serious jeopardy due to the rapid emergence and global spread of microorganisms that are resistant to antimicrobials.

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[1] Consult the latest version of the Vision paper (currently from April 2011) for more detailed and current information.
[2] Priority Medicines for Europe and the World, Kaplan W, Laing R. Geneva: World Health Organization (2004).
[3] Goldstein FW. Penicillin-resistant *Streptocuccus pneumoniae*: selection by both beta lactam and non-beta lactam antibiotics. J Antimicrob Chemother 44:141-144 (1999).
[4] COMMISSION STAFF WORKING DOCUMENT *accompanying the* COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL on patient safety, including the prevention and control of healthcare-associated infections. SEC (2008) 3004.
[5] EMEA/ECDC estimates based on bacteria most frequently isolated from blood cultures in Europe. The bacterial challenge: time to react. ECDC/EMA joint technical report. European Centre for Disease Prevention and Control (2009).
[6] Conference report; Innovative Incentives for Effective Antibacterials (2009).

The problem of drug resistance is a natural and unavoidable consequence of treating infectious diseases with antimicrobial drugs. However, this is exacerbated by indiscriminate use of antimicrobials and dissemination of antibiotic-resistant bacteria in the environment. Migration of human populations, travel and worldwide distribution of food significantly contribute to the rapid spread of resistant infectious microorganisms[7]. Moreover, the misuse of antibiotics in livestock increases the risk of spread of resistant microorganisms to humans through food consumption[8] and the environment. In addition, the development of new antimicrobials is declining dramatically.

Cross-border collaboration is essential given that the increasing resistance of microorganisms to antibiotics is not confined to single countries, but poses a real threat to public health on a global scale. Sharing the burden to efficiently handle the challenges ahead will yield benefits for all countries involved, and will allow for better management and treatment of infectious diseases in the future.

While excellent research is being carried out throughout Europe, the current European landscape for AMR research appears to be rather complex and fragmented. Many research networks and organisations at European and national level define AMR research agendas in isolation, leading to overlaps or competing research activities that often lack a critical mass. The EU has been supporting research addressing AMR since the 5th Framework Programme and the scope and budget for this research have increased over time.

In order to address the problems, on the one hand, and realise the opportunities for innovation, on the other, these research efforts would benefit from centralised coordination and from a unified platform for information exchange. The coordination of the best European research resources and capabilities will form the necessary critical mass and develop the most advanced scientific approaches to tackle the problem of AMR, reverting its increasing trend, and leading to sustainable use of antibiotics and treatments for infectious diseases. AMR is a global challenge. A comprehensive solution to the problem requires measures from many sectors of society – policy-makers, healthcare, education, industry, environmental agencies, agriculture, veterinary medicine, research, and other areas.

The JPI "The Microbial Challenge – An Emerging Threat to Human Health" offers an opportunity to bridge fundamental knowledge and cooperation gaps, not only between researchers in different countries but also between researchers and other stakeholders, such as industry, healthcare services organisations and professionals, patient organisations and policy-makers.

Although the proposed JPI alone will not solve the problem, it will be a starting point for reducing the fragmentation of research efforts of Member States and will step up the mobilisation of skills, knowledge and resources, with a view to advancing and strengthening Europe's leadership and research competitiveness in this field. The JPI may lead the way forward by producing new research and creating networks that can create long-term momentum for other areas in society and contribute to the development of a global strategy.

This staff working document reflects the status of programmes and initiatives, and is likely to be updated with the development of the SRA of the JPI.

[7] World health report 2007. A safer future: global public health security in the 21st century. WHO (2007).
[8] Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections. EFSA Journal 7(11):1372 (2009).

## II. Towards Joint Programming

In its communication of 15 July 2008, entitled "Towards joint programming in research: Working together to tackle common challenges more effectively"[9], the Commission called for the implementation of a process led by Member States to step up their cooperation in the R&D area in order to better confront major societal challenges, in Europe and worldwide, where public research plays a key role. Thereafter, with the Council conclusions of 2 December 2008[10], the dedicated configurations of CREST and the High Level Group for Joint Programming (GPC) were established, with a view to identifying and substantiating the first list of a limited number of joint programming themes. The pilot JPI on "Combating Neurodegenerative Diseases, in Particular Alzheimer's" was launched with the Council conclusions of 3 December 2009[11], which also welcomed the identification and substantiation of the first wave of themes for JPIs in the areas of "Agriculture, Food Security and Climate Change", "Cultural Heritage and Global Change: A New Challenge for Europe", and "A Healthy Diet for a Healthy Life". The six 'second wave' JPI themes[12], which include "The Microbial Challenge – An Emerging Threat to Human Health", were identified and substantiated in the Council conclusions of 26 May 2010[13].

The first preparatory meeting for "The Microbial Challenge – An Emerging Threat to Human Health" took place in Stockholm on 9 February 2010. A total of 43 experts, including both scientists and representatives from governmental institutions from 15 European Member States and Associated Countries participated. A second meeting with the working group was held on 6 April 2010, and the proposal was then formally proposed by GPC delegates from Sweden and Italy. Within its mandate, the GPC recommended starting such a joint programme, and the proposal was supported by the Council of Ministers in May 2010.

A kick-off meeting was held on 20 October 2010, after which Member States and Associated Countries were encouraged to nominate members for an interim Management Board (MB) to initiate the establishment of a governance structure. Fourteen countries (Czech Republic, Denmark, Finland, France, Greece, Italy, Norway, Poland, Romania, Spain, Sweden, Switzerland, Turkey, the United Kingdom) nominated members, and since then, three more have joined the initiative (Belgium, Germany and the Netherlands). The nominating countries were also asked to submit national interest statements to be able to start outlining the scientific direction, and to build a common vision and mission for the JPI "The Microbial Challenge – An Emerging Threat to Human Health".

At the first meeting of the MB on 9 December 2010, decisions were made on a governance structure that included the MB, a Steering Committee (SC), a Scientific Advisory Board (SAB), a Stakeholders Advisory Board (SHAB) and a Secretariat. At the same meeting, a chair, Sweden, and a vice-chair, Spain, were selected. An appointed working group presented the outline of a potential Vision Document and it was decided to hold a scientific workshop during the spring of 2011 to receive input from the scientific community on the SRA and the scientific direction of the JPI. The second MB meeting took place on 3 February 2011. Decisions were taken to adopt the Terms of Reference document as discussed at the previous meeting (Appendix I), as well as a procedure to map research activities within the field. The third MB meeting was held on 14 April 2011. The direction of the JPI was further outlined by the approval of the Vision Document[1] and the adoption of the process for electing the SAB members.

[9] Communication 11935/08.
[10] Official Journal C 24, 30.1.2009, p. 3–6.
[11] Communication 17226/09.
[12] 'Connecting Climate Knowledge for Europe (Clik'EU)', 'Healthy and Productive Seas and Oceans', 'More Years, Better Lives - The Potential and Challenges of Demographic Change', 'The Microbial Challenge - An Emerging Threat to Human Health', 'Urban Europe - Global Challenges, Local Solutions' and 'Water Challenges for a Changing World'
[13] 10246/10.

A first scientific workshop was held on 2-3 May 2011 to ensure the commitment of the scientific community and to assist in setting the focus on the necessity, added value and future actions. Representatives from the European Commission were invited to and attended all of the meetings. Thereby, the initiative has received input directly from Commission representatives and the Member State delegates have been able to follow the progress within the JPI. Within the envisioned developments, the SAB is to be established and is then expected to draw up the future SRA, beginning in September 2011.

The Vision Paper of the Initiative was drafted based on the proposal that was submitted to the GPC on 21 April 2010. It was released in April 2011, elaborating on the societal needs, the research priorities of the initiative, and the expected results and policy benefits of the JPI. The Vision Paper also established the holistic nature, the reference framework and visionary objectives in order to relate them to R&D and policy-making issues. The Vision Paper reiterates the three main focus areas of the JPI: (1) Biology and dynamics of resistance; (2) Prevention of resistance and innovation of treatment options; and (3) Epidemiology and disease burden. It stresses the readiness to develop strong relations between academia, policy-makers, and other public and private stakeholders in order to effectively tackle the multidimensional challenge of combating AMR and its threat to human health. The Vision Paper has been elaborated on and approved by the 17 participating Member States and will form the basis for the SRA of the Initiative. The SRA will aim to identify the research goals (in a 5 year plan) and is to be reviewed regularly in order to integrate new findings.

The governance structure of the JPI will ensure appropriate guidance to achieve the objectives within the working areas mentioned above.

## *1. Governance structure*

The JPI Governance structure that has been decided on includes a MB, an SC, a SAB, a SHAB and a Secretariat. The MB, the SC and the Secretariat are already installed and the process of nominating and electing members to the SAB is ongoing. There is currently an interim structure, but as soon as the Commission recommendations have facilitated a positive conclusion by the Council, a permanent structure will be adopted.

*Management Board*
Each participating country can nominate up to two members for the MB. Only one representative for each country may vote. Presently, an interim MB has been set up, working according to the Terms of Reference that have been established.

*Steering Committee*
The SC assists the MB by preparing meetings, proposals for actions and strategy, allowing the MB to focus on strategic decisions. It also oversees the work of the Secretariat and specifies the tasks to be carried out by it. In order to ensure continuity, the SC will be composed of the Chair, former Chair, Vice Chair and two other members from the MB chosen by consensus or by voting, if necessary.

*Secretariat*
The Secretariat will be hosted by an appropriate organisation in one of the participating countries. The functions of the Secretariat include making necessary arrangements for the meetings within the management structure, assisting the different boards with the preparation of documents as well as compiling reports and other documents (e.g. minutes of the meetings). Presently, the Secretariat

is hosted by the Swedish Research Council, which has committed to providing the necessary resources for the first few years.

*Scientific Advisory Board*
The SAB should consist of 12 to 15 members, nominated on personal merit, irrespective of nationality. They shall be elected among the most pre-eminent scientists in the field and their independence and integrity shall be beyond doubt. Further, they have to be recognised leaders in the relevant fields, as well as have an understanding of the organisational and operational setting of transnational cooperation. The SAB members will be nominated and elected by the MB members. The election procedure of the SAB has been established.

*Stakeholders Advisory Board*
Since AMR is a problem spanning many different fields of society, a SHAB is of particular interest to this JPI. The SHAB will be included in the governing structure in order to secure input from relevant stakeholders, but also in order to keep these stakeholders informed of the activities within the JPI. Potential members of the SHAB include representatives from pharmaceutical companies, public health organisations, patient organisations, and business and non-business organisations.

To further emphasise the importance of continued and expanded relations with the pharmaceutical industry, the MB appointed a working group, with the special task of identifying relevant pharmaceutical companies and to establish contacts.

# III. Antimicrobial Resistance State of Play

## *1. Why is Research Needed?*

Modern healthcare has come to depend largely on the use of drugs to combat infectious microorganisms and it is anticipated to increase even further with the ageing population and increasing global infection rates. However, the more frequently we use these drugs, the less effective they will become in the long run.

AMR is no longer simply a potential threat; it is a serious health problem that is already upon us and is accelerating rapidly. Today, we are witnessing the results of decades of antibiotics use and misuse, and have a duty to future generations to rectify the mistakes made. The European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO) consider antimicrobial drug resistance to be one of the major health threats in Europe in the 21st century[14].

In the EU, about 4 million patients are estimated to acquire a healthcare-associated infection each year[15]. According to a recent report from the ECDC and the European Medicines Agency (EMA), more than 25,000 patients die in the EU each year from infections caused by a limited group of healthcare-associated bacterial infections resistant to multiple antibiotics, so-called multiple drug-resistant (MDR) bacteria and 400,000 are infected[16]. This number is likely to be significantly underestimated. In addition to healthcare costs, infectious diseases caused by resistant bacteria result in indirect costs, such as sick-leave and output lost due to premature death. Indeed, the report

[14] Priority Medicines for Europe and the World (2004). Kaplan W, Laing R, Geneva: World Health Organization.
[15] COMMISSION STAFF WORKING DOCUMENT *accompanying the* COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL on patient safety, including the prevention and control of healthcare-associated infections. SEC (2008) 3004.
[16] EMEA/ECDC estimates based on bacteria most frequently isolated from blood cultures in Europe. The bacterial challenge: time to react. ECDC/EMA joint technical report. European Centre for Disease Prevention and Control (2009).

by ECDC/EMA estimated these at €1.5 billion/year. However, the indirect costs to European countries are likely to be several-fold higher. To avoid epidemics caused by MDR strains, costly control and prevention measures need to be taken. This cost includes not only staff directly in charge of infection control but all the dedicated personnel of the ward during an epidemic. Other costs are those of the microbiology lab, which has to identify the bacteria in the infected patients and also in all of the people the patient came into contact with during the epidemic. Another indirect cost is that no new admissions of patients may well occur during an epidemic, due to the need to isolate patients or even close down entire wards.

Resistance rates to a single antibiotic exceed 50% in several European countries, and resistance to multiple antibiotics is a common and increasing problem[17]. In healthcare settings, AMR notably represents a threat of particular concern. Infections resistant to antimicrobial drugs are among the most common cause of healthcare associated infections, i.e. infections occurring after exposure in a hospital or a healthcare service unit.

It should also be emphasised that AMR is not something that only concerns sick people and patients. Healthy people carry antimicrobial-resistant bacteria on their skin and in their intestines, throat, etc. These resistant strains, predominantly bacteria, may be spread to more susceptible, vulnerable people. Hence, the problem of AMR can affect every European citizen, and no one is exempt.

Bacteria have developed resistance to almost every antibacterial developed in the past decades, starting with penicillin. The development of resistance is a naturally-occurring, evolutionary phenomenon, which can be exacerbated in a number of ways: i) there is a positive correlation between the use of antibiotics and the development of resistance; ii) inappropriate use of antibiotics, e.g. as treatment for viral infections; iii) the use of broad spectrum antibiotics rather than targeted narrow spectrum antibiotics; iv) non-adherence to the treatment regime; v) the misuse of antibacterials in farming and aquaculture; vi) spread of antibiotic-resistant bacteria in the environment. Resistant pathogens may spread across microorganisms as well as humans, animals and the environment. Food and direct contact with animals (both food producing and companion animals) may serve as a vehicle for the spread of resistance from animals to humans, emphasising the link between human and veterinary medicine. It needs to be recognised that globalisation, with increased movement of people and animals, and global distribution of food, contributes to an increased speed of resistance development and spread.

A gap between the increasing problems related to bacteria resistant to antibiotics and the need for developing new antibiotics to meet medical needs in human medicine has been identified. Firstly, the poor investment returns on research in this therapeutic area are considered to be the main reason for the lack of the pharmaceutical industry's involvement in the development of new antibiotics. Secondly, development of novel antibiotics poses a major scientific challenge. It has been estimated that an average of 20 late-stage drug candidates are needed to yield one marketable antibacterial drug. It was hoped that sequencing of bacterial genomes would boost the discovery of novel antibiotics, but it has been reported[18] that the success rate for antibacterial high throughput screening is four to fivefold lower than for targets for other therapy areas.

In essence, the JPI "The Microbial Challenge – An Emerging Threat to Human Health" proposes utilising the potential of R&D as a cornerstone in defining challenges and opportunities, providing

[17] EMEA/ECDC estimates based on bacteria most frequently isolated from blood cultures in Europe. The bacterial challenge: time to react. ECDC/EMA joint technical report. European Centre for Disease Prevention and Control (2009).

[18] Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL (2007). Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nature Reviews Drug Discovery 6:29-40.

new knowledge as the basis for policy-making and defining new research fields. It views the need to safeguard the currently available antimicrobials and the need to develop novel ones as a great societal challenge that needs to be addressed by pooling research efforts in Europe in order to make better use of the available resources.

The research questions that are being addressed by this JPI focus on three main areas. Firstly, the JPI aims to understand the biology and dynamics of resistance, which is of prime importance for controlling the emergence and spread of resistant infectious organisms. Secondly, it aims to improve disease prevention, support development of novel antimicrobials and refined treatments, alternative treatments, and rapid diagnosis of pathogens and their resistance profiles. Finally, it aims to increase the knowledge of the global prevalence and spread of different infectious microorganisms and to estimate the financial and societal burden of disease.

This initiative is very timely as it will provide a complementary element to the Europe 2020 policy and its priority on the Innovation Union by tackling a major societal challenge in cooperation between Member States and providing new underpinning scientific knowledge to address the microbial challenge.

The need to improve coordination of research on the implications of the microbial threat in Europe between Member States and with the EU Framework Programme is evident, in particular considering the importance of this common societal challenge and the current fragmentation of efforts between disciplines and between Member States. Few countries appear to have a programme addressing AMR; rather, countries are financing separate projects that have been selected in competition with projects from other research areas. The coordination effort of the JPI will help to overcome this fragmentation by integrating relevant scientific fields across national borders and creating a common European research agenda, with a shared common vision. The knowledge generated will support policy-making and will improve the overall quality of research and innovation in the field.

# IV. Mapping of Programmes

## *1. Country Programme Focus*

Before decisions can be made on the priorities that should be made within the JPI "The Microbial Challenge – An Emerging Threat to Human Health", it is important to conduct a mapping of ongoing European research activities within the field of AMR and to better understand the different structures in place to support research on AMR at national level as well as countries' involvement in international initiatives on AMR. A first "light" mapping exercise was therefore carried out by the JPI Secretariat.

Two different arms of mapping have been initiated within the JPI, one focusing on research funders and the other focusing on active researchers. Questionnaires were sent out to principle investigators (PIs) within the participating countries as well as to major national research funders. At the MB meeting on 3 February 2011 it was decided that the mapping should cover research within the three modules described in the original JPI proposal, but that only research on bacterial resistance should be included, not viruses and parasites. The PIs in each country were identified by the MB representatives for that country with the help of their National Expert Panels (NEPs).

Most of the national financing organisations allocate funding to research projects on AMR through open, competitive grants. However, only a few international networks or collaborations dedicated to the problem of AMR were mentioned (the major international programme of relevance for

AMR is ERA-NET "PathoGenoMics"; however, this programme spans a much broader field and is only partly dedicated to research on AMR). Furthermore, the great majority of the investigated organisations stated that they lack a defined research strategy for AMR research (notable exceptions are Dutch ZonMW and German BMBF). It is, thus, clear that there is a strong need for coordination of European research in the field of AMR. A JPI is an excellent opportunity to accomplish such coordination.

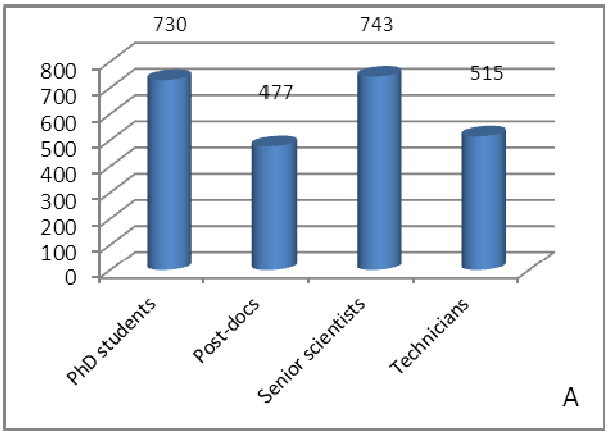
A questionnaire was sent out to 506 principal investigators active in the field of antibiotic resistance. It has to be stressed that this is probably not all the researchers active in the antibiotic resistance field in the participating countries, but most likely the majority have been reached. Also, several PIs that had received the questionnaire contacted the secretariat asking it to be sent to colleagues relevant for the survey. The addressees were asked to provide relevant background information as well as to list their activities within the field of antibiotic resistance. In order to avoid overlap, they were specifically asked to only report staff and projects for which they were the PI. Regarding their active projects, they were asked to provide information on budget, duration and scientific orientation, and also to state what their funding sources were. More than 300 PIs responded to the questionnaire, resulting in a response rate of 70%. This high response rate may well be viewed as an indication of the interest and engagement of the scientific community within the antibiotic resistance field.

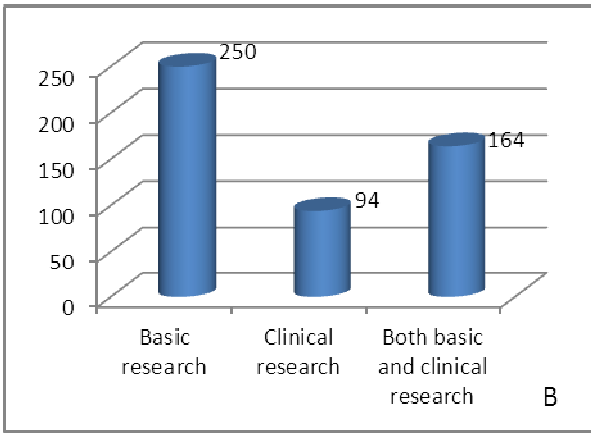
***Manpower:*** 316 PIs provided an answer to the question regarding their staff resources. The numbers of PhD students, postdoctoral fellows, senior scientists and technicians reported in the survey can be found in Fig. 1A. In total, this adds up to almost 2500 scientists and staff engaged in these projects.

***Budget of projects:*** 300 researchers reported at least one project, and in total 600 projects were reported. Most PIs, but not all, reported the budgets and duration of their projects. The total budget of 536 reported projects was €284 million. When analysing the duration of the projects, it could be concluded that the total annual budget of 490 reported projects was €63 million. A more thorough analysis of the funding sources that have been reported will reveal in more detail where the funding comes from. Amongst the sources that have been specified are grants from national research funders, governmental block grants, EU grants, as well as contributions from private funding agencies and industry.

***Scientific direction of projects:*** The PIs were requested to select the most appropriate alternative describing their projects regarding basic versus clinical research. They were also asked to choose the most appropriate module out of the three modules described in the original proposal: biology and dynamics of resistance, prevention of resistance and novel treatment options, and epidemiology and burden of resistance. The results of these questions are presented in Figs 1B and 1C. The reported projects were quite evenly divided between the three modules, with a little more in the first one and a little less in the last one. Most of the projects were regarded as being basic research (49%), followed by those regarded as concerning both basic and clinical research (32%). A quick scan of the projects considered to be both basic and clinical research reveals that many of them focus on surveillance and epidemiology.

In the last question regarding scientific content, the PIs could choose between about 50 keywords describing the projects. The keywords selected 25 times or more are given in Fig. 2. What can be noted is that most of the keywords relating to the second module (prevention and novel treatment options) end up amongst the least selected ones (including *therapy*, *prevention of hospital infections*, *natural products*, *antimicrobial peptides*, *clinical trial*, *vaccine*, *bacteriophage*, *bacteriolysins*, *immunomodulation*, *immunotherapy*, *probiotic* and *monoclonal antibodies*), while the terms related to the description of the problem are amongst the most frequently selected ones.



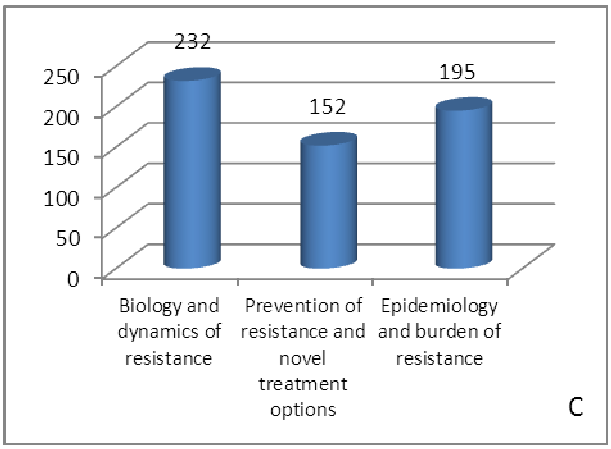
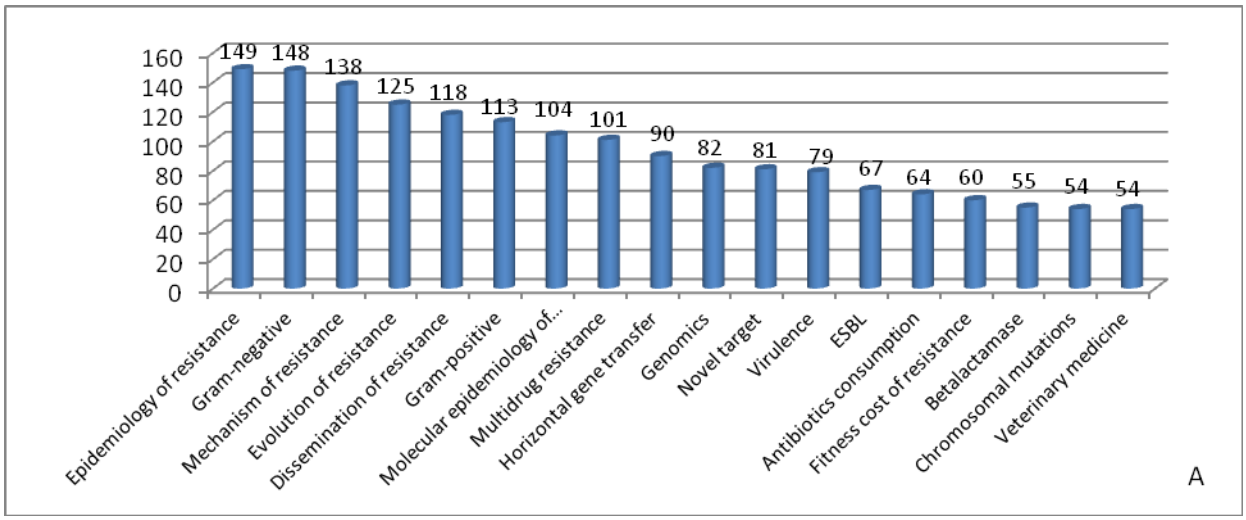




**Figure 1. Results of the researchers' survey.** A) The number of staff in different categories reported by 316 principal investigators. B) The number of projects that were reported to be basic research, clinical research or both. C) The number of projects that were reported to belong to each of the scientific modules that have been identified in the JPI "The Microbial Challenge – An Emerging Threat to Human Health".

***Networks and programmes***: The PIs were asked to list networks that they participated in. The most frequently mentioned networks were ESCMID – European Society of Clinical Microbiology and Infectious Diseases, EUCAST – European Committee for Antimicrobial Susceptibility Testing, ERA-NET PathoGenoMics, ESAC – European Surveillance Antibiotic Consumption, EARS-NET – European Antimicrobial Resistance Surveillance Network and GRACE – Genomics to Combat AMR.



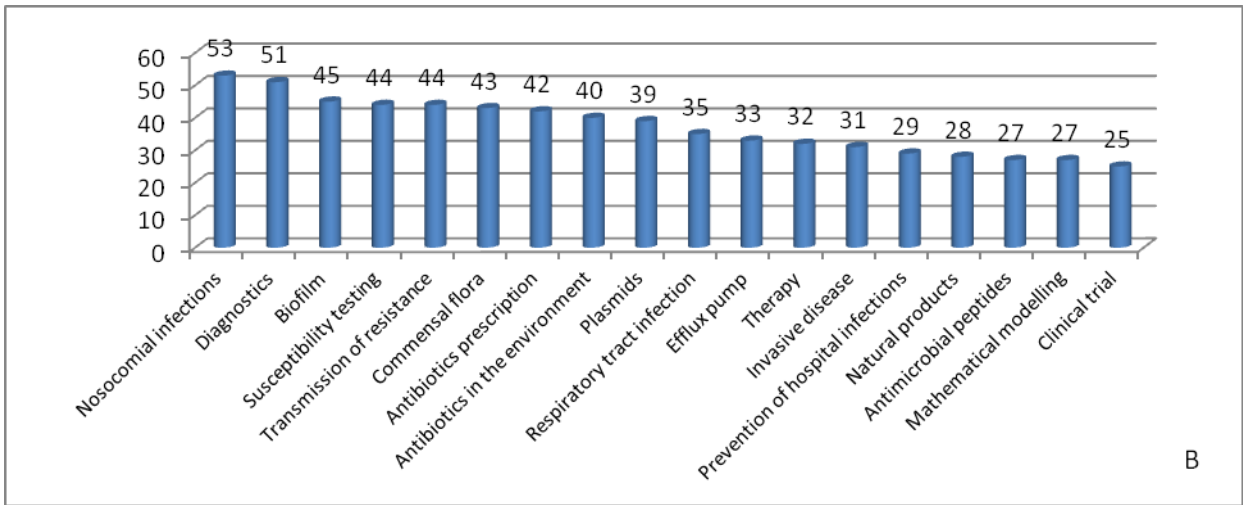



**Figure 2. Results of researchers' survey.** For each project, the PIs could choose up to five keywords (out of 50) describing the project. This figure shows the keywords that were selected 25 times or more. The 18 most frequently selected keywords are found in part A, while the next 17 are found in part B.

Below is a summary for each country participating in the JPI "The Microbial Challenge – An Emerging Threat to Human Health" that includes an outline of the structure for AMR policy-setting and the main funding structures in place where support for research can be obtained, as well as the country's involvement in major EU or international networks on AMR.

## Belgium

In Belgium the Federal Public Service (FPS) Health, Food Chain Safety and Environment is responsible for antibiotics policy and sanitary risks. FPS finances both targeted research projects and free research projects. In 2009, more than €500,000 was assigned to 2 projects with a total duration of 7 years concerning antimicrobial resistance in food and related to animal health. For the call in 2010, project proposals had to address specific themes related to the safety of the food chain, health policy for animals, and plant and animal welfare. The Belgian Antibiotic Policy Coordination Committee (BAPCOC) informs on the use of antibiotics.

The CODA-CERVA (Veterinary and Agrochemical Research Centre) is a Federal scientific research establishment. Its core activities consist of scientific research, expert advice, efficient provision of services in veterinary activities, epidemic, endemic and emerging transmissible diseases in animals, zoonotic and emerging infectious diseases threatening public health, epidemiology: surveillance, risk analysis, and molecular epidemiology, agrochemical activities, contaminants and the quality of the environment in the framework of safe food production. It contributes to a proactive policy in terms of food production safety, animal health and public health, at both the Federal and international levels. It supports the preparation of the FPS Health, Food Chain Safety and Environment and of the Federal Agency for the Safety of the Food Chain (FAFSC). CODA-CERVA is under the wardship of the Minister of SMCs, Independent workers, Agriculture and Scientific policy, and is administratively connected to the FPS Health, Food Chain Safety and Environment. CODA-CERVA employs about 75 researchers, some 105 laboratory technicians and approximately 50 people in support services.

The reference laboratory for infectious diseases in animals has 3800 m² of confinement level 2 laboratories (Biosafety level 2 or BSL-2) to identify endemic infectious diseases and BSE, as well as 2150 m² of confinement level 3 laboratories (BSL-3), comprising: reference laboratories for aphthous fever (foot-and-mouth disease) also vesicular diseases, plague virus, influenza and avian and exotic viruses, also for highly-pathogenic bacterial diseases (plague, anthrax, brucellosis, tuberculosis, tularaemia, etc.); a bacteriology laboratory to identify emerging or incipient risks

(new infectious diseases, bioterrorism). In addition, there is 3600 m² of confinement level 3 animal houses 3 (BSL-3) for small laboratory animals, poultry, ruminants and pigs. CODA-CERVA publications on the subjects: "Antibiotic resistance surveillance and emergence of cephalosporine resistance" and "MRSA"[19].

Research and Innovation policy is mainly under the responsibility of the regional governments. In Flanders, the Department of Economy, Science and Innovation is responsible for research policy. There are no thematic research programmes in Flanders, only horizontal (bottom-up) programmes. Basic research is funded by the Research Foundation - Flanders (FWO). There are two ongoing FWO-funded research projects relevant to 'antibiotic resistance' with funding of €484,500. The total duration of these two projects is 7 years. The total amount for projects funded in the entire domain of medical sciences in 2010 was €24.771 million. Strategic and applied research in Flanders is funded by the governmental agency for Innovation by Science and Technology (IWT). As FWO, IWT finances excellent research projects on a competitive basis, including projects concerning microbial resistance. IWT is also involved in two ERA-net projects with relevance to the life sciences sector, including microbial resistance: EuroTransBio and Industrial Biotechnology. In Wallonia, it is the Service Public de Wallonie - Direction générale opérationnelle de l'Economie, de l'Emploi et de la Recherche" (DGO 6) that is responsible for research policies. As in Flanders, the Fund for Scientific Research (FRS- FNRS) funds basic research in French-speaking universities.

Antimicrobial research in Belgium can be divided into four broad areas with the following aims: (1) To develop integrated point-of-care platforms for critical infections to rapidly detect bacteria, mycobacteria, and related antibiotic resistances that would allow a timely institution of adequate therapy that by itself would limit subsequent morbidity and mortality; (2) To identify biomarkers that might serve as potential targets for new antimicrobial therapies or as diagnostic/prognostic markers; (3) To obtain in-depth knowledge of bacterial resistance mechanisms that are not related to the presence of resistance gene markers, such as biofilm and persister cell formation, which would facilitate development of therapeutic options for recalcitrant infections; (4) To study the impact of antibiotic usage on development of drug resistance in the human host at the gene, genome and microbiome levels to allow important insights on the selection potential of commonly used antibiotics and the impact on human infectious disease of human commensal flora as well as of pathogen burden in the environment

Belgium participates as well as coordinates several EU projects funded by DG Research in FP6 and FP7, as well as IMI-JU (RAPP-ID, in collaboration with EFPIA partners), DG SANCO (ARPEC) and ECDC (EARS-Net and ESAC-Net). Finally, several international research and capacity building programmes involving antimicrobial resistance issues specifically related to developing countries in Africa and Asia are also being funded by the Flemish Interuniversity Council (VLIR-UOS).

## Czech Republic

In the Czech Republic, three Ministries are of relevance for AMR – the Ministry of Health (MoH), the Ministry of Agriculture (MoA) and the Ministry of Education, Youth and Sports (MEYS). The MEYS holds the budget for public research funding agencies, including the Academy of Sciences of the Czech Republic (ASCR). However, neither the MEYS nor the ASCR have significant specific programmes focused on tackling AMR and control of multi-resistant microorganisms.

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http://www.var.fgov.be/index.php?option=com_content&view=article&id=408%3Aantibioresistance&catid=200%3Alatest-topics&Itemid=263&lang=en

These institutions award single grant proposals in competition with other scientific areas (of biological and medical sciences), performed by various institutions (i.e. National Institute of Public Health, medical faculties, University of Veterinary and Pharmaceutical Sciences Brno, Institute for State Control of Veterinary Biologicals and Medicines, etc.). Besides smaller project grants, no broader initiatives in the field of AMR have been supported in recent times. The MoH holds another budget for research through the Internal Grant Agency (IGA). The issue of AMR is mentioned in the ministerial "Conception of Applied Health Research and Development for 2010-2015"[20]. Nevertheless, only short-term projects concentrated on mechanisms of development of AMR have been funded. To our knowledge, there is presently no major research on AMR through any of the above mentioned channels; however, there is also another source of funding, the so called Biennial Collaborative Agreement between the MoH and WHO. In the agreement for 2010-2011, the "Tools for improved rational drug prescribing in primary care" project is funded (total budget: $6000).

During the Czech Presidency of the EU Council in 2009, the issue of preventing and controlling AMR and healthcare-associated infections in hospitals was included among the main priorities in the field of public health protection. Consequently, the Czech Presidency presented a "Proposal of Concept Framework and Measurable Elements for Hospital Antibiotic Stewardship Programmes"[21] as one of its main outcomes. After the end of the Presidency, several achievements were reached. In December 2009, the MoH (based on Resolution No. 595/2009 of the Czech Government) established the National Antibiotic Programme (NAP) and specified its scope, objectives, activities, functions and organisational structure. In accordance with the contents and targets of the Council Recommendation on the prudent use of antimicrobial agents in human medicine (2002/77/EC), the 15-member Central Coordination Group (CCG), in which representatives of human as well as veterinary medicine are involved, was established as an advisory body of the MoH to govern the NAP. The CCG members are appointed and removed by the Minister of Health, based on a written proposal submitted by the institution whose representative the member is. NAP activities are conducted at all levels in accordance with the Action Plans where the priorities for a 2-4 year period are defined. Based on the CCG proposal, every Action Plan is approved by the MoH in cooperation with the MoA and implemented in collaboration with so called antibiotic centres. The network of the antibiotic centres was created from the bottom up in the 1970s and contributed to promoting the prudent use of antibiotics. These organisational units were incorporated into clinical microbiology departments and were made responsible for local surveillance of AMR and supervision of the use of "restricted" antimicrobials. The network of antibiotic centres has remained active until the present time and currently represents a local structure ready for use in organising further interventions. The Contemporary Action Plan for 2011-2013[22] was approved by the MoH in March and by the Czech Government in April 2011. In general, all NAP activities are funded from the limited budget of the National Institute of Public Health (NIPH) and no other funding sources have been allocated yet (this issue is amongst eleven priorities of the Action plan for 2011-2013). NIPH is trying to search for other sources of funding (i.e. European Regional Development Fund (ERDF), EEA Grants and Norway Grants, Framework Programme, etc.).

In 2012, NIPH plans to finish its project (funded by ERDF) – inspired by the Belgian and French public awareness campaigns – focused on the creation of "systemic tools for public health promotion and prevention of health risks", in which €290,000 is allocated on prevention of AMR and overuse (and misuse) of antimicrobials. Moreover, a public contract focused on development of an information system for the National Reference Laboratory for Antibiotics (based in NIPH) is

[20] See page 21 of http://www.mzcr.cz/Odbornik/Soubor.ashx?souborID=6750&typ=application/pdf&nazev=Koncepce_PDF.pdf.
[21] http://czpres.mzcr.cz/Categories/640-Hospital-Antibiotic-Stewardship-Programme-(H-ABS-Programme).html
[22] http://www.szu.cz/uploads/AP_NAP_2011_2013.pdf

currently in preparation. This system will connect microbiological laboratories participating in the EARS-Net project (ca. 55 participants from ca. 70 antibiotic centres), and thus enable more systematic and reliable data collection for national and ECDC's use (this project is also funded by ERDF).

The Czech Republic is involved in EARS-Net, ESAC, EUCAST, HELICS (now ECDC's HAI-Net), and other international collaboration is coordinated through the NAP Secretariat.

## Denmark

In Denmark, three Ministries are involved in antibiotic policy and research: The Ministry of Interior and Health, the Ministry of Food, Agriculture and Fisheries, and the Ministry of Science, Technology and Innovation. The two former ministries in collaboration fund the Danish antibiotic resistance and consumption monitoring programme (DANMAP), which has published an annual report since 1997[23]. Funding for this programme also involves research on antibiotic resistance, its relationship to antibiotic use in both the human and veterinary field, and the risk of transfer of resistant bacteria from animals to humans. DANMAP is run as a collaboration among the following institutions: Statens Serum Institut, Danish Veterinary and Food Administration, Danish Medicines Agency, National Veterinary Institute, Technical University of Denmark and National Food Institute, Technical University of Denmark. The Danish Medicines Agency is involved in this programme as a provider of antibiotic consumption data both in humans and to animals (VETSTAT). The human resistance data to the programme are provided in collaboration with the clinical microbiology laboratories in Denmark (presently 14) and organised via the DANRES collaboration. The resistance data on the veterinary side are collected from the above veterinary institutes from food products and production animals.

The antibiotic policy programme supervising the DANMAP collaboration is now led by the Antibiotic Board (Antibiotikarådet), headed by the National Health Board (under the Ministry of Interior and Health), with representation of all of the above institutes as well as members of several medical specialty societies and the veterinary medical society.

Research funding on a competitive level is provided, first of all, through the Danish Agency for Science, Technology and Innovation, and its different subdivisions, e.g. the Danish Council for Strategic Research or the Danish Council for Independent Research. There have been various calls from the strategic research council during the last decade providing funding for research in this area, e.g. DanCARD, a collaborative programme for research into new antimicrobials and improvement of antibiotic therapy involving 11 research institutions at various universities and the Statens Serum Institut (approximately €4 million). Private foundations have also provided some funding for research on antibiotic resistance and related issues (the Velux foundation, the Cystic Fibrosis association and others). Various Danish research groups are partners in several EU FP-projects as well as in projects funded by the National Institutes of Health (NIH).

Denmark is involved in several international networks dealing with antibiotic resistance issues, such as EARS-Net, ESAC and EUCAST. Furthermore, international research programmes involved in AMR issues related to malaria, tuberculosis and bacterial pathogens in general in third world countries, particularly Africa, are ongoing and funded by the Danish Agency for Science, Technology and Innovation, by DANIDA (the Danish Development Aid organization under the Ministry of Foreign Affairs of Denmark).

Since there are no active antibiotic research programmes in any of the major Danish pharmaceutical companies, such as Novo, Leo Pharma or Lundbeck, private funding via these

[23] www.danmap.org

companies is to our knowledge scarce. Some smaller Danish biotech companies are involved in privately funded projects related to resistance issues.

## Finland

In Finland, four Ministries have activities linked to antibiotic policy, AMR surveillance and research: The Ministry of Social Affairs and Health, the Ministry of Agriculture and Forestry, the Ministry of Education, and the Ministry of Employment and the Economy.

The National Institute for Health and Welfare (THL) is a research and development institute under the Finnish Ministry of Social Affairs and Health, with activities linked to surveillance and research on infectious diseases and antibiotic resistance in humans. THL runs the National Infectious Disease Register with surveillance data on multiresistant bacteria and harbours several national reference laboratories. THL also coordinates the activities of the Finnish Study Group for Antimicrobial Resistance which is a coalition of the Finnish clinical microbiology laboratories and the bacteriology units of THL.

The Finnish Medicines Agency (Fimea) is the national competent authority to regulate pharmaceuticals and to provide data on antibiotic consumption in humans. Fimea operates under the Ministry of Social Affairs and Health.

Similarly, the Finnish Food Safety Authority (Evira), from the administrative field of the Ministry of Agriculture and Forestry researches and monitors animal health and welfare, as well as diseases capable of passing from animals to humans (zoonoses) including antibiotic resistance. The FINRES-Vet programme, which monitors veterinary AMR and consumption of antimicrobial agents is coordinated by Evira, in collaboration with Fimea.

The Academy of Finland is the prime funding agency for basic research (including antibiotic resistance) in Finland. The Academy operates within the administrative sector of the Ministry of Education. There have been no specific calls from the Academy of Finland during the last decade providing funding for research in this area. Other key agencies funding science and technology in Finland are the Finnish Funding Agency for Technology and Innovation (Tekes), which operates under the Ministry of Employment and the Economy, the Finnish Innovation Fund (Sitra). Private foundations have also provided some funding for research in antibiotic resistance and related issues. Various Finnish research groups are partners in several EU FP-projects.

Finland is involved in several international networks dealing with antibiotic resistance issues, such as EARS-Net, ESAC and EUCAST.

There are no active antibiotic research programmes in the only Finnish pharmaceutical company, namely Orion. Some smaller Finnish biotechnology companies are involved in privately funded projects related to resistance issues (diagnostics or drug development).

## France

In France, two ministries are relevant for AMR: the Ministry of Higher Education and Research (MESR) and the Ministry of Labour, Employment and Health (MTES).

The MESR holds the budget for the National Funding Agency (ANR) - €185 million in 2010 for biology and health - and the research organisations. The ANR has no specific programme within the field of AMR but rather awards single projects in competition with other scientific areas following a bottom-up principle. All the research organisations in health (CEA, CNRS, INRA, INRIA, INSERM, Institut Pasteur, IRD, medical research centres and universities) form the national alliance called AVieSan. AVieSan is composed of 10 thematic institutes among which the

Infectious Diseases Institute (IMMI) has identified AMR as one of the major priorities in its SRA. The dedicated research teams are listed in the JPI mapping. The large programme "investment for the future" (€22 billion for higher education and research) launched in 2010 by the MESR is funding two projects on infectious diseases: the Institute University Hospital (IHU) POLMIT, in Marseille, for research, care, training and technology transfer in the field of infectious diseases and the Institute of Technology Research (IRT) Lyon Biotech, that will strengthen the ecosystem formed by the cluster Lyonbiopôle, through public-private strategic partnerships in research, training and innovation.

The MTES finances monitoring agencies, such as INVS and ANSES, to coordinate the networks of surveillance of bacterial resistance to antibiotics. INVS collects data from several specific pathogen reference centres and also supports a devoted reference centre for AMR, the network of surveillance of hospitals or cities, and reporting of nosocomial infections (Raisin). ANSES monitors AMR in animals using the reference centres' networks for AMR (LNR and Resapath). The surveillance of multi-resistant bacteria is reinforced by the collaborative effort of microbiologists that constitute ONERBA. Moreover, the MTES is launching the third national strategy for prudent use of antibiotics. Clinical research is funded by a specific programme named PHRC with around €700,000 per year for AMR.

Furthermore, France has a strong industry in the field, with e.g. Sanofi Pasteur for the discovery of drugs and vaccines, BioMérieux for diagnosis and the SMEs of the cluster Lyonbiopôle.

French research teams are strongly committed to FP7 with significant participation in FP7-funded projects. ANR is the French partner for several transnational programmes including the ERA-NETs, PathoGenoMics and ERA-Infect (as a coordinator). French experts and agencies are working closely with European and international networks and agencies concerned by AMR, such as EARSS, ECDC or WHO.

## Germany

The most relevant Federal Ministry in Germany for research funding in the field of AMR is the Federal Ministry of Education and Research (BMBF). The BMBF holds the budget for the relevant public funding agencies, PT-DLR (Project Management Agency – part of the German Aerospace Centre) and PtJ (Project Management Jülich). In addition, the German Research Foundation (DFG) funds relevant projects in the field of basic research. There are several specific programmes dedicated to infectious diseases that are funded by the BMBF, covering – among other topics – the topic "antimicrobial resistance", for example:

- German centre for Infectious diseases (one of six German centres for health research; the total funding volume for the next 5 years for health research is approx. €700 million)
- Research on zoonotic diseases (collaboration of the BMBF with the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV); BMBF funding volume from 2007 to 2013 approx. €52 million)

There is no dedicated AMR funding initiative, but a "German AMR strategy" was elaborated in 2008 by the BMBF in collaboration with the German Federal Ministry of Health and the BMELV. This national AMR strategy accounts for AMR in humans as well as animals. A detailed description (in German) can be downloaded[24]. The Federal Ministry of Health and the BMELV are responsible for policy-making on antibiotics issues.

[24] http://www.bmg.bund.de/fileadmin/dateien/Downloads/A/Antibiotikaresistenzstrategie/DART_Zwischenbericht_110407.pdf

Germany is involved in two ERA-NETs with relevance to AMR: PathoGenoMics and Emerging and Major Infectious Diseases of Livestock (EMIDA)/Animal Welfare. In addition, Germany participates in several European networks dealing with antibiotic resistance problems, e.g. EARS-Net.

## Greece

The General Secretariat for Research and Technology (GSRT) was founded in 1985. GSRT is the central department for the administration of the Greek R&D system. It is the main policy-maker and programme owner concerning the R&D system in Greece. GSRT's policy is implemented through operational programmes, the current one having a duration of six years (2007-2013). Through its programmes, it supports the research activities of both the country's scientific research institutes and those of its productive industry, focusing on areas that are important for the national economy and for the improvement of quality of life; it promotes the transfer and dissemination of advanced technologies throughout the country's productive sector, thus ensuring early utilisation of the results of research activity; it contributes to the reinforcement of the country's research manpower; it represents Greece in relevant institutions of the EU, thus bringing the country's research and technology activities into line with the requirements of the international community; it promotes cooperation with other countries and international organisations on research and technology issues; it establishes new institutes and technological centres in support of sectors of high priority for the development of the Greek economy; it supervises and underwrites the fixed costs of, and otherwise provides support for 21 of the country's best-known research and technological centres; it supports the dissemination of research and technology information throughout the country and internationally by means of advanced IT systems and networks; it encourages activities aimed at raising awareness of the general public about research and technology issues.

GSRT has no specific programme within the field of AMR but awards single projects in competition with others in the scientific field of biomedical research in a bottom-up approach. There are research teams in the Medical Schools of the University of Athens and the Aristotle University of Thessaloniki and the Hellenic Pasteur Institute with important activities in the study of resistance mechanisms of microorganisms to antibiotics.

The Greek System for Surveillance of Antimicrobial Resistance is a national network for continuous monitoring of bacterial antibiotic resistance in Greek hospitals. Its function is based on the assumption that the routine results of antibiotic sensitivity tests performed daily in each hospital clinical laboratory should be considered as a major resource for antibiotic resistance surveillance. Moreover, and since the quality and compatibility of these data are in principle uncertain, our approach is to work in parallel, on both accessing the data and assessing its quality. This is accomplished through the establishment of a quality control procedure and the adaptation of an electronic code and data format in all hospitals through the use of the WHONET software. WHONET is distributed free of charge by WHO/EMC and facilitates the management of antibiotic susceptibility test results from routine clinical isolates. The analysis of the information facilitates: (1) Understanding the trends of resistance; (2) Detecting epidemics; (3) Differentiation of epidemic from endemic infections; (4) Development of a national antibiotics policy; (5) Setting priorities for further studying the genetic and molecular mechanisms responsible for the emergence of resistance. Moreover, and since the acquisition of the data is performed automatically, no additional workload at the laboratory level is generally required, and thus the system can function on a routine basis. The WHONET software is being adopted as the common programme, because it is user-friendly, flexible, allows an easy pyramidal reporting structure and is capable of interfacing with other statistical packages and programmes. This enables each laboratory to configure its result entry format to its own testing practices and to the specific patient locations it

serves. The file format for all laboratories, however, is universal, so a common analytical procedure is in use in all of the laboratories.

The Greek System for Surveillance of Antimicrobial Resistance participates in EARSS, is sponsored by the Hellenic Centre for Disease Control and Prevention (HCDCP), in the framework of the scientific alliance between the National School of Public Health and the Hellenic Centre of Infectious Disease Control and Prevention, is under the supervision of the Infectious Control Committee of HCDCP, and is coordinated by the Department of Microbiology, National School of Public Health, and the Department of Microbiology, Medical School, Athens University.

## Italy

Two Italian Ministries are of special relevance for AMR: the Ministry of Health (MoH) and the Ministry of Education, Universities and Research (MIUR).

The MoH holds the budgets for the National Board of Health and Welfare, responsible for policy-making in questions related to antimicrobial drugs and their usage in human and animals. Inside this Ministry, the General Directorate for Prevention funds surveillance and research projects, including the network, AR-ISS, that monitors antibiotic resistance in bacteria from human infections and contributes data to the European Surveillance EARS-Net. Data from AR-ISS surveillance are published in a special report every three years and are available yearly on the EARS-Net website. The Department of Veterinary Public Health, Nutrition and Food Safety is involved in policy-making and in promoting prudent use of antibiotics in veterinary medicine and along the food chain. Monitoring of AMR in zoonotic and indicator bacteria in primary production is provided annually according to harmonised EFSA guidelines and EU legislation (Commission Decision 407/2007/EC), through the network of the Regional Veterinary Institutes (Istituti Zooprofilattici Sperimentali, IZSs), coordinated by the National Reference Laboratory for Antimicrobial Resistance (IZS Latium and Tuscany, Rome, Italy). Each year, data on AMR in bacteria of animal origin (i.e. major zoonotic bacteria such as *Salmonella* and *Campylobacter* and indicator bacteria) are reported at the national level, and data and comments on the current situation are uploaded onto the zoonoses website[25], and become part of "The European Union Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Food-borne Outbreaks"[26] and of other scientific reports, such as "The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from animals and food in the European Union"[27].

The MIUR holds the budget for the public Universities and Research Institutes, other than those under the MoH, such as the Italian Research Council (CNR). Some of these organisations fund research within the field of AMR. Neither of the two Ministries have specific programmes within the field, but rather award single projects in competition with other scientific areas following a bottom-up principle.

Italy is involved in several European networks dealing with antibiotic resistance issues, e.g. EARS-Net and EUCAST in the human field, and in monitoring of AMR in primary production and food of animal origin in the veterinary field (harmonised monitoring at EU level according to EFSA guidelines and European Commission legislation).

[25] https://zoonoses.efsa.europa.eu/zoonoses/zoonose
[26] http://www.efsa.europa.eu/en/efsajournal/pub/2090.htm
[27] http://www.efsa.europa.eu/en/efsajournal/pub/2154.htm

## The Netherlands

The Netherlands' Ministry of Health, Welfare and Sport commissioned the WHO in 2003 to study the need for new medicinal products in relation to the burden of disease. The WHO concluded that the increasing resistance to existing antibiotics (AMR) in Europe and elsewhere in the world was a very serious problem. The WHO stated in its final report (Priority Medicines for Europe and the World, November 2004) that combating resistance and developing new antibiotics was of the highest priority. The Netherlands has accepted these conclusions and recommendations. The country had already developed various methods to combat resistance and mobilised medical professionals to implement these methods and other recommendations. However, there is also an urgent need to develop new antibiotics, a need that is recognised worldwide by scientists in the field, by the pharmaceutical industry and by the medical profession. The Netherlands has, following the Priority Medicines report, organised meetings with relevant stakeholders in the areas of infectious (i.e. bacterial) diseases (epidemiologists, microbiologists, treating physicians) and scientists from learned institutions and from the pharmaceutical industry. The consultations resulted in a proposal for a scientific programme, to be funded by the government (the Ministry of Health, Welfare and Sport) and to be put under the auspices of the Netherlands organisation for health research and development (ZonMw). The Ministry accepted this proposal in 2008. The name of the programme, Priority Medicines Antimicrobial Resistance, is a tribute and a reminder of the well-known report issued in 2004.

The Ministry of Health, Welfare and Sport stated, at the time of the consultations, the main themes regarding a prospective for a programme. These were then further developed into the actual scientific programme. Currently, the Ministry is represented at meetings of the programme committee by an observer. The observer is, however, in no way involved in decisions regarding submitted proposals. The governance of this programme is under the auspices of the programme committee and ZonMw.

To help control AMR and to foster the development of new antimicrobials, ZonMw opened up the research programme Priority Medicines Antimicrobial Resistance. ZonMw will fund basic and applied research over a period of nine years (2009-2018), with a total budget of €14.8 million. The programme's focus is on antibacterial resistance, but research that concerns AMR in viruses or fungi is also considered for funding, to a limited extent. In a programming study, five research areas were identified: (1) The role of antimicrobial use in inducing and transmitting resistance; (2) Mechanisms and targets for new drugs; (3) New technologies, in particular rapid diagnostics; (4) Optimising antimicrobial therapy: dosage and use; (5) Innovative approaches in AMR prevention.

The development of new drugs or vaccines has no place in the programme, although the discovery of new points of action for drugs or vaccines is clearly a part of this research programme. For all research areas, the methodology of infectious disease modelling is considered of particular value. As a systematic and overarching approach to the control of infectious disease, it can help identify knowledge gaps and facilitate policy decision making. The Ministry stressed the link between human and animal AMR, and emphasised the importance of the collaboration with the Ministry of Agriculture in the preparation of the research programme and beyond. So far, two calls for proposals have been launched and a third (last one) will be launched in 2012. Currently, the proposals, submitted after the second call, are under evaluation. For more detailed information regarding the programme, the reader is referred to consult the relevant website[28].

## Norway

The NORM surveillance programme for AMR in human pathogens was established in 1999 and is coordinated by the Department of Microbiology and Infection Control at the University Hospital of

[28] http://www.zonmw.nl/en/programmes/all-programmes/priority-medicines/

North Norway in Tromsø. The NORM-VET monitoring programme for AMR in the veterinary and food production sectors was established in 2000 and is coordinated by the Norwegian Zoonosis Centre at the National Veterinary Institute. The use of antimicrobial agents in humans and animals is based on wholesalers' data reported to the Norwegian Institute of Public Health. This reporting was made mandatory from 2002.

AMR is still a limited problem in Norway. The relatively low use of antimicrobial agents as well as the advantageous patterns of use must be maintained to preserve this favourable situation. The data presented in the 2009 NORM-VET report show that Norwegian antimicrobial policies in food production and healthcare have succeeded. However, the situation may rapidly change if the use of antimicrobial agents in Norway increases or resistant clones are imported from abroad. A continued effort is needed to prevent the development and spread of AMR and, thereby, ensure the effectiveness of antimicrobials when such treatment is needed.

The National strategy for prevention of infections in the health service and antibiotic resistance (2008–2012) is a result of cooperation among five Norwegian ministries: the Ministry of Labour and Social Inclusion, the Ministry of Fisheries and Coastal Affairs, the Ministry of Agriculture and Food, the Ministry of the Environment, and the Ministry of Health and Care Services (MoH). The strategy includes relevant measures in many sectors and at various levels that should enable us to continue to maintain a favourable situation in Norway.

In general, public funding of medical and health related research comes through four channels: (1) Grants to the Regional Health Authorities from the MoH; (2) The Research Council of Norway receives part of its funding from the MoH; (3) The National Institute of Public Health is a subordinate institution under the MoH and receives its core funding from this ministry; (4) The Ministry of Education and Research funds medical and health research through universities and colleges through their core funding. This ministry also funds medical and health-related research through grants to the Research Council of Norway. In addition, NGOs such as the Norwegian Cancer Society, "Health and Rehabilitation", and the commercial sector fund medical and health related research. At present, there is, to our knowledge, no earmarking for research on antibiotic resistance through any of these channels. However, research on antibiotic resistance can be funded through channels 2 and 3 described above.

## Poland

In Poland, two Ministries are of relevance for AMR: The Ministry of Science and Higher Education and the Ministry of Health.

The Ministry of Science and Higher Education holds the budget for the public funding agency, the National Centre of Sciences. Neither the Ministry nor the Centre have major specific programmes within the field of AMR but award single grant proposals in competition with other areas of biological and medical sciences, performed by various institutions (National Medicines Institute, National Institute of Public Health, Medical Universities, National Veterinary Institute etc.).

- Besides shorter term (1-3 years) projects, the Ministry supports the ongoing project of National Collection of Microorganisms (MIKROBANK) that has been running since 1995 (annual budget €50,000-100,000), located at the National Medicines Institute. MIKROBANK comprises collecting, characterising and storing major human bacterial pathogens, responsible for a variety of infections, with a special emphasis on MDR organisms. These strains are representative of the whole country.
- The Institute of Immunology and Experimental Therapy in Wroclaw of the Polish Academy of Sciences conducts a programme on experimental treatment in patients in whom no effective available antibiotic therapy exists or the use of the targeted drug is contraindicated. The programme is called "Experimental phage therapy of drug-resistant

bacterial infections, including MRSA infections". It is carried out at the Phage Therapy Unit – the Institute's outpatient clinic and it enables the use of bacteriophages (bacterial viruses which are able to kill antibiotic-resistant bacteria) from the Institute's collection under the rules of a therapeutic experiment (on the basis of the respective Polish regulations: law on the physician's profession, pharmacological law, regulations of the Minister of Health). The Institute is part of a consortium with the Medical University of Warsaw and the Institute of Biochemistry and Biophysics, Polish Academy of Sciences in Warsaw within the framework of a grant from the Polish Ministry of Science and Higher Education, supported by funds from the Operational Programme Innovative Economy, 2007-2013 (OP IE): *"Optimization of the production and characterization of bacteriophage preparations for therapeutic use"* with a budget of €3.8 million. OP IE is one of the six National Strategic Reference Framework programmes which are financed by the European Regional Development Fund and the nation.

The Ministry of Health is responsible for the application of several EU directives, concerning the containment of AMR (ICM). Within this responsibility, the Ministry has been supporting a specific ongoing programme, the National Programme of Antibiotic Protection (NPOA) since 2004 with an annual budget of around €180,000. The programme covers a variety of activities, coordinated by the National Medicines Institute, including education of primary care and hospital-based physicians, social campaigns on European Antibiotic Awareness Day (EAAD), elaboration of evidence-based therapeutic recommendations and laboratory diagnostic guidelines, as well as some targeted antibiotic resistance and consumption surveillance. In addition, the Ministry finances a programme complementary to NPOA (NPOA-MODUŁ), dealing with the surveillance of community-acquired invasive bacterial infections and resistance (annual budget varies from year to year, around €200,000). Since recently, NPOA-MODUŁ also covers surveillance of healthcare-associated infections, comprising educational activity focused on medical personnel (antibiotic stewardship in hospital, hospital antibiotic formulary and PPS). Poland is involved in several European networks dealing with antibiotic resistance questions, e.g. EARS-Net, Seq-Net and EUCAST.

## Romania

The Ministry of Education, Research, Youth and Sports[29] holds the budget for the public funding agency called UEFISCDI-Executive Unit for Superior Learning Financing, and for Research, Development and Innovation. Research projects are monitored and financed through UEFISCDI. There is no specific programme in the field of AMR, but there are awarded projects in competition with other scientific areas in the health domain. The following are national projects that were financed by UEFISCDI in the programme "National Plan I and II" (2007-2013), in the field of AMR:

1. Contract No. 41003/2007: Evaluation of the molecular profile of influenza virus regarding antiviral resistance and clinical relevance. Leader: The National Institute of Research and Development for Microbiology and Immunology, Cantacuzino (INCDMIC), Bucharest.
2. Contract No. 41018/2007: Generation of micro-nanoparticles that contain antibiotics exposed on laser radiation with the purpose of overpass the resistance at treatment. Leader: The National Institute of Research and Development for Physics of Lasers, Plasma and Radiation, Bucharest.
3. Contract No. 41048/2007: Multicentric monitoring of antibiotic resistance. Impact on recommendations of the recent antibiotherapy. Leader: The Institute of Infectious Diseases "Prof. Dr. Matei Bals", Bucharest.

[29] www.edu.ro

4. Contract No. 42094/2008: Diarrheal syndromes caused by Enterobacteriaceae in children of 0-4 years. Molecular studies of diagnosis, pathogenicity, virulence and antibioresistance. Leader: The University of Medicine and Pharmacy Carol Davila, Bucharest.
5. Contract No. 42150/2008: Intersectorial research regarding clarifying new aspects of antibioresistance with major impact in cardiovascular surgery and gastroenterology. INCDMIC, Bucharest.

The Ministry of Health (MoH)[30] holds the budget for National Health Programmes, one of which is the National Programme of Antibioresistance Surveillance. Within the MoH, there is one specialised department, Public Health and Control in Public Health Direction, responsible for the national control of transmissible diseases, nosocomial infections and antibioresistance. Two public institutes are subordinated to the MoH and play key roles in the National Programme of Antibioresistance Surveillance:

1. The National Institute of Research and Development for Microbiology and Immunology "Cantacuzino" (INCDMIC) includes National Reference Laboratories, one of these being the Laboratory of Nosocomial Infections and Antibioresistance. This laboratory coordinates antibiotic resistance inside the National Programme of Antibioresistance, including microorganisms isolated from invasive infections, in accordance with EARSS protocols. This laboratory collaborates with the other national reference labs from INCDMIC (Bacterial Enteric Infections Lab, Bacterial Respiratory Infections Lab, Fungus Infections Lab) and with other laboratories from Romania. INCDMIC drafts guidelines and protocols for nosocomial infections testing and antibiotic sensitivity testing for microorganisms. It participates in external quality control within EARSS, receiving reference strains, and exchanging data and materials with collaborative laboratories outside INCDMIC.

The National Institute of Public Health, Bucharest (INSP) contains a structure called the National Centre of Evaluation and Promotion of Health Status (CNEPSS), which has a role in defining and implementing antibioresistance strategies, in compliance with the Community Strategy against AMR of 2001.

Romania has participated in EARSS since 2002. Although the number of participant laboratories has increased progressively from 12 to 35, the number of reporting labs has remained constant and low. Since 2005, Romania has included a Sentinel Programme of Nosocomial Infections Surveillance and one objective was to evaluate antibioresistance. Since 2009, the MoH has become more involved in events regarding information and education on antibioresistance, for example, European Information Day for Antibiotics (18 Nov. 2010), Press Conference "Resistance to antimicrobial agents" (7 April 2011). Also, the Romanian Microbiology Society organised the "National Conference on Microbiology and Epidemiology" (14-16 Oct. 2010), with one area being antibioresistance

## Spain

The Ministry of Science and Innovation is in charge of the National Research/Development/Innovation Plan. The “Strategic Action on Health” is part of this Plan, and is managed by the Institute of Health Carlos III (ISCIII), acting as the health research funding agency of Spain. This Strategic Action funds two sorts of initiatives:

- *Health research projects*, also including funding for research infrastructures and for human resources. There is no specific budget item for infectious or any other group of diseases, and grants are awarded according to evaluation scores. Around €500,000 are awarded to projects on antibiotic resistance per year.

[30] www.ms.gov.ro

- *Health research structures*, including research networks. The most interesting network for AMR is REIPI[31], with the participation of 21 hospitals (mostly teaching hospitals), 3 universities, 2 centres of the High Council for Scientific Research, and 1 of the "intramural" centres of ISCIII (National Centre for Microbiology). Most of their scientific agenda is directly or indirectly related to AMR, such as use of antimicrobials, MRSA, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, design and evaluation of new antimicrobials. REIPI receives around €1 million per year in funds.
  Another interesting network is CIBERES[32], working with respiratory diseases, which includes a programme on pathogen-host interactions in resistant microorganisms. There is also CIBERESP[33], a network on public health research that develops research on AMR. CIBERs receives four or five times more funding than REIPI, but it is difficult to identify how much of this is invested in AMR.

As for health policy related to AMR, it is responsibility of the Ministry of Health, Social Policy and Equity. ISCIII contributes with its specialised expertise, including the National Centre for Microbiology (CNM) as the reference centre, and chairs the national network of laboratories and surveillance system. Over 70,000 invasive individual isolates from 40 hospitals have been registered so far. During the last decade, Spain has been an active member of the European surveillance systems on AMR (EARS-Net) and antibiotic consumption (ESAC). These systems are based at the CNM – ISCIII. CNM – ISCIII has also been part of the Trans-Atlantic Task Force on AMR (TATFAR), in collaboration with ECDC.

## Sweden

In Sweden, the Ministry of Education and Research holds the budget for the public research funding agencies, including the Swedish Research Council (VR), VINNOVA and Formas. All of these organisations fund research within the field of AMR (about €1 million per year and agency). None of them have specific programmes within the field, but rather award single projects in competition with other scientific areas following a bottom-up principle. Besides smaller project grants, two larger AMR initiatives have been supported during the last five years:

1. Umeå Centre for Microbial Research (UCMR) Linnaeus Programme: A VR-funded project granted €1 million per year for 10 years. UCMR is an interdisciplinary consortium of academic research groups with the goal to develop new anti-virulence control strategies for microbial infections.
2. Predict, prevent and diagnose antibiotic resistance: A VINNOVA-funded project granted €2.5 million over 6 years within the "Innovations for future health" programme.

The Ministry of Health and Social Affairs is in charge of the National Board of Health and Welfare, responsible for policy-making in antibiotics questions, as well as the Medical Products Agency (MPA), the national authority responsible for approval and continuous surveillance of efficacy and safety of medicinal drugs and other medicinal products, in close cooperation with other EU regulatory authorities. In addition, the MPA provides independent information to prescribers and pharmacy staff, and also arranges regular conferences where leading experts draw up treatment recommendations, such as for common infectious diseases. This Ministry also holds the budget for the Swedish Institute for Communicable Disease Control (SMI) that coordinates surveillance of antibiotic resistance. The Swedish strategic programme against Antibiotic Resistance (Strama) is an advisory organ to SMI and is involved in policy-making on, for example, the prudent use of antibiotics. Its sister organisation, Strama-VL, handles the same questions on the veterinarian side and is coupled to the National Veterinary Institute (SVA) (under the Ministry for

[31] http://www.reipi.org/inicioE.html
[32] http://www.ciberes.org/index.php?perfil=portada
[33] http://ciberesp.es/web

Rural Affairs). Each year, SMI and SVA publish the SWEDRES/SVARM reports on antibiotic usage and resistance, covering both the human and the veterinarian side. The Swedish Reference Group of Antibiotics (SRGA) and its subcommittee on methodology (SRGA-M) are the expert groups on antibiotics of SMI, Strama and the Swedish Association of Medicine. They are involved in the work of determining MIC- and zone diameter breakpoints for new antibiotics and continuously revise breakpoints of older antibiotics. Sweden is involved in several European networks dealing with antibiotic resistance questions, e.g. EARS-Net, NordicAST and EUCAST. It is also the administrative home of ReAct, an independent global network for concerted action on antibiotic resistance. ReAct is organised as a project funded by a number of Swedish agencies, but predominantly by the Swedish International Development Cooperation Agency. ReAct acts as a forum for ideas, debate and collaboration between various stakeholders and coordinates specific activities and concerted action planning with these groups. ReAct also plays a leading role in EU level discussions on future policies to combat AMR.

## Switzerland

In Switzerland, two Ministries are of special relevance for AMR: the Federal Department of Home Affairs (FDHA) and the Federal Department of Economic Affairs (FDEA). FDHA holds, with its State Secretariat for Education and Research, the budget of the Swiss National Science Foundation (SNSF), while FDEA feeds the more applied research oriented Innovation Promotion Agency. None of them have specific programmes within the field, but rather award single projects in competition with other scientific areas following a bottom-up principle. Besides smaller project grants, one larger AMR initiative has been supported in the past: The National Research Programme 'Antimicrobial Resistance' (NRP 49). This SNSF-funded programme granted CHF 12 million from July 2001 through June 2006. The programme intended to focus on establishing scientific strategies and new methods applicable to a prospective system of resistance monitoring and on the analysis of the current situation concerning resistance in Switzerland in all relevant areas (human and animal populations, agriculture, foodstuffs and the environment). Parts of this 5-year programme are ongoing, e.g. the Swiss Centre for Antibiotic Resistance (ANRESIS).

Both ministries also play an important role in policy-making and implementation: while, for example, Swissmedic and the Federal Office for Public Health (FOPH) are affiliated to FDHA, the Federal Offices for Veterinary and Agriculture are affiliated to FDEA. Together, they run, for example, the Antibiotic Sales and the Antibiotic Resistance Monitoring programmes (ARCH-VET). In addition, FOPH mandated and supports the National Antibiotic Resistance Reference Centre as a part of ANRESIS, which was one of the big projects within NRP 49. The law of epidemics, which is currently under revision, is expected to build a further legal base for combating antibiotic resistance.

Switzerland is involved in several European networks dealing with antibiotic resistance questions, e.g. EARSS, ESAC and ESVAC, or projects.

## Turkey

The Scientific and Technological Research Council of Turkey (TUBITAK) founded in 1963, is the leading agency for management, funding and conducting of research in Turkey. TUBITAK is the only organisation involved in research and surveillance within the AMR field. TUBITAK's mission is to develop scientific and technological policies in line with national priorities and in cooperation with all sectors (including the field of AMR) and related establishments; contribute to establishment of infrastructure and instruments to implement said policies; support and conduct research and development activities; and to play a leading role in the creation of a science and technology culture with the aim of improving the competitive power and prosperity of the country.

TUBITAK not only supports innovation, academic and industrial R&D studies but also, in line with national priorities, develops scientific and technological policies and manages R&D institutes, carrying on research, technology and development studies. However, there are no specific programmes within the AMR field. Single projects are rather awarded in competition with other scientific areas following a bottom-up principle. From 2006-2010, TUBITAK supported 11 projects, with a total budget of approximately €417,600 (835,300 TL) for the AMR field. The AMR grant budget is 0.18% of TUBITAK's related departments' (TBAG & SBAG) total budget.

The Bilateral and Multilateral Relations Division under the TUBITAK International Cooperation Department is responsible for carrying out or monitoring the below-mentioned activities of bilateral cooperation and cooperation with international organisations. These programmes are divided into three general categories: (1) Bilateral cooperation; (2) Cooperation with regional and international organisations; (3) Cooperation with the EU, including the European Framework Programme. There are also single projects in the field of AMR under these international programmes following bottom-up and top-down principles.

## United Kingdom

Three Government departments in the UK oversee organisations that fund research into AMR: the Department for Business, Innovation and Skills (BIS), the Department of Health (DH), and the Department of Food and Rural Affairs (Defra), which also funds research into AMR in animals and veterinary medicine.

The seven UK Research Councils (including the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC)) are publicly funded and receive their budgets through BIS. Both MRC (€3.4 million/year) and BBSRC (€2.1 million/year) fund research in the field of AMR.

Responsibility for AMR policy and funding within Defra is shared between the Food and Farming Group of Defra (FFG) and the Veterinary Medicines Directorate. Current investment in evidence for veterinary medicines, including AMR in 2011-2012 is £2,461,500 of which £2,158,000 is for R&D and £303,500 is for surveillance of certain aspects of AMR.

DH also supports policy development, surveillance and funding for clinical research within the National Health Service.

DH allocates the budget to the Health Protection Agency (HPA, currently a Non-Departmental Public Body), which has the aim of protecting the public from threats to their health from infectious diseases and environmental hazards, including AMR. Surveillance for disease and AMR is a central role of the HPA and its advice, information and services are underpinned by evidence-based research. MRC and BBSRC do not fund surveillance.

There is also large investment in the UK from the Wellcome Trust, a global charitable foundation dedicated to achieving extraordinary improvements in human and animal health. The annual funding for AMR research is estimated to be €10.4 million.

The MRC, BBSRC and Wellcome Trust do not have specific research programmes in the field, but award funding through responsive mode, initiatives and fellowships, and core strategic funding to institutes where appropriate.

BBSRC is a member of the Defra Antimicrobial Resistance Co-ordination Group which advises on how the Department can best contribute to the knowledge on and understanding of the role of

MRSA in animals, in the light of the increasing number of reports in animals and the increasing concern about MRSA in the public health sector.

BBSRC is also one of the partners of the EMIDA ERA-Net. The scope of the EMIDA ERA-Net includes emerging and major infectious diseases of production animals, including fish and bees, and including those conditions which pose a threat to human health but excluding food safety issues relating to livestock products and diseases of wildlife, except where they act as reservoirs of infection for humans or production animals. The EMIDA ERA-Net has launched two transnational calls which included AMR as a priority research topic.

In 2007, the MRC, in partnership with 6 other UK research funders (BBSRC, Wellcome Trust, DH (England), Health and Social Care Research and Development Public Health Agency (Northern Ireland), Chief Scientist Office Scottish Government Health Directorate and National Institute for Social Care and Health Research (Welsh Assembly Government)) under the auspices of the UK Clinical Research Collaboration (UKCRC) launched the UKCRC Translational Infections research Initiative (TIRI). UKCRC TIRI aimed to establish a number of consortia to boost capacity for translational research in the field of microbiology and infectious diseases. Four such consortia were funded from 2008-2010/11 at a total cost of £14 million and each has a component of research relating to AMR as part of their research programme.

In 2008, the MRC and the Canadian Institutes of Health Research Institute of Infection and Immunity launched the Canada-UK Joint Partnership on Antibiotic Resistance. The Partnership aimed to build on existing collaborations by providing support for consortia tackling the problem of antibiotic resistance. Phase 1 awarded two Catalyst Grants in 2009 and Phase 2 was launched in September 2010, with the aim that joint Canada-UK consortia combine the research strengths in both countries to provide a true value-added collaborative effort that will advance our approach to antibiotic resistance along the translational pipeline from biomedical research to clinical practice. Two Consortia Grants were funded in May 2011 at £2 million each, funded 50:50 between the MRC and CIHR, each consortium consisting of a UK and a Canadian team.

## *2. European Level Initiatives*

### a) Policy Dimension

As mentioned above, the JPI "The Microbial Challenge – An Emerging Threat to Human Health" aims at providing a better scientific basis for a coordinated policy response to the emerging and increasing problem of AMR.

In 1998, the "The Microbial Threat" conference in Copenhagen was attended by a broad range of stakeholders across the veterinary and human medical sectors, industry, regulators and policy-makers to discuss, for the first time in a comprehensive fashion, the emerging threat of AMR. This conference was groundbreaking in that it opened up a dialogue that is still ongoing in Europe and has helped to bring Europe to the forefront in terms of effective interventions, legislation (in the veterinary sector) and general awareness of AMR.

From 2000 onwards, there were several EU Presidency initiatives, which often included a major Presidency Conference and the subsequent development of a set of Council Conclusions or Recommendations, each on a slightly different aspect of AMR in humans (prudent use of antibiotics, infection control, hygiene etc.) as a main focus and driven by national ministries of health with the Directorate-General for Health & Consumers (DG SANCO) as the main Commission entry point. The role of the EU Framework Programmes for Research and

Development (FP5-FP7) was to provide continuous support to relevant research, which is crucial for making progress on the recommendations.

To address the public health concern posed by AMR, over the years the Commission has developed a series of EU-wide policy and legislative initiatives for the prevention and control of AMR:

In 2001, the Commission presented its 15-point Community Strategy against AMR that called for EU initiatives against AMR in the fields of surveillance, research, prevention and international cooperation. This led to the adoption of EU-wide recommendations and guidelines against AMR, charging Member States to report back to the Commission on progress made.

Council Recommendation 2002/77 on the prudent use of antimicrobial agents in human medicine lays out specific actions to be implemented by Member States and the Union, with a view to containing AMR. This includes the establishment of the European Surveillance of Antimicrobial Consumption (ESAC) Network which maintain a database on human antibiotic use in Europe[34] and build on existing surveillance systems for AMR, notably the European Antimicrobial Resistance Surveillance System (EARSS), later EARS-Net[35]. Furthermore, it addresses the implementation of control measures, the promotion of education and training programmes for healthcare workers, and improvements in informing the public about the importance of the prudent use of antimicrobial agents.

A recent Commission report[36] on the implementation of this Recommendation has highlighted important progress with regard to Member States having or adopting national strategies and action plans against AMR. However, only limited improvement has been made in: i) the setting up of appropriate mechanisms for the coordinated implementation of these recommendations; ii) restricting antibacterial agents to prescription only use; iii) promotion of the prudent use of antimicrobial agents in long-term care facilities; iv) improving the level of education of healthcare professionals and the public; and v) monitoring the evaluation of the national strategies.

On 10 June 2008, the Council adopted Conclusions on AMR calling upon the Commission, in accordance with the "health in all policies" approach, to promote mutual cooperation between different services of the Commission, Agencies and the Member States against AMR.

In the veterinary sector, guidelines by international organisations, veterinary associations as well as by Member States for the use of antimicrobials have been developed. However, no EU-wide follow-up has taken place. Some Member States have also put in place various measures, legislative and others, to promote appropriate use. In animal husbandry, a ban on the use of antimicrobials for growth promotion was introduced in 2006. In the field of veterinary medicine, the emphasis has been on monitoring zoonotic (i.e. resistance transmissible between animals and humans) AMR and in the use of antimicrobials in animals. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) was established in 2009. Ongoing work to develop a new EU Animal Health Law will provide the legal tool to enhance prevention and control of infections in animals. Improved animal health, biosecurity measures and promotion of Good Farming Practices may contribute to the reduction of the need to use antimicrobials in animals and consequently the development of AMR. The authorisation requirements of human and veterinary medicines and other products, such as food enzymes, probiotics and decontamination agents, with possible effects on the development of AMR, have also been policy focus areas.

[34] http://app.esac.ua.ac.be/public/
[35] http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx
[36] http://ec.europa.eu/health/antimicrobial_resistance/docs/amr_report2_en.pdf

The One Health strategy, that was put forward by the Commission as part of the Animal Health Strategy for the European Union (2007-2013), facilitates the setting up of a joint (Commission, Member States) strategic framework for reducing the risks of infectious diseases at the interface between animals and humans. One Health provides a cross-sectoral and multidisciplinary approach for issues which are inextricably linked to animal health, such as public health, food safety, animal welfare, sustainable development and research. In the area of AMR, the Animal Health policy addresses the provision of more incentives to manufacturers to develop new medicines and diagnostic tools, as well as the surveillance and control of AMR in zoonotic agents by the use of antibiotics in animals.

The 2009 Commission staff working paper on AMR (SANCO/6867/2009r6) summarised initiatives on AMR at EU level. Several follow-up actions, e.g. improved monitoring of AMR and antimicrobial usage and further risk management measures, were proposed in the public consultation in 2010. All these proposals have been further strengthened by a series of Council Conclusions and Parliamentary resolutions ensuring political commitment at EU level against AMR.

The Commission is preparing concrete measures to combat AMR and its consequences for public and animal health in the coming years.

After the establishment of the ECDC and thanks to its resources, the European collaboration on AMR has been reinforced and the initiatives have become more ambitious. The most tangible successes are the well prepared national antibiotic awareness campaigns, supported by the ECDC (in collaboration with the European Commission). Along with the development of national strategies for the prevention and control of AMR, these campaigns have helped to bring down, not only excessive antibiotic use (with the associated savings), but have also managed, in some cases, to reduce drug resistance (especially MRSA, less so for other bacterial species). Moreover, as of 2008, an EU-wide European Antibiotic Awareness Day (EAAD) is organised every year on 18 November by the ECDC to support Member States' national awareness-raising campaigns. A different theme and target group is chosen for each EAAD.

### b) Research programmes, projects

The EU has been strongly committed to combating AMR since 1999, and has prioritised research in this field over several Framework Programmes (FP5-FP7). Since then, almost €600 million have been awarded to AMR projects. Further details of these projects are provided in Appendix II. In FP7, these research projects have been supported through the Health, and Food, Agriculture and Fisheries, and Biotechnology (FAFB) themes of the Cooperation programme of FP7 (managed by the European Commission's Directorate-General for Research & Innovation (DG RTD)), and through the Ideas programme (managed by the European Research Council[37], which was set up in 2007 to support investigator-driven frontier research). The vast majority of projects are managed by the Health Directorate of DG RTD. These projects aim to form and support multidisciplinary collaborations, obtain a critical mass of researchers investigating AMR within Europe and mobilise the European biotech industry[38].

Research on AMR began in 1999 during the 5th Framework Programme (FP5, 1998-2002). More than €104 million were awarded to around 80 projects that were funded primarily through the Quality of Life programme. The projects covered a large number of different bacterial, fungal, protozoan and viral target pathogens known to generate drug resistance problems of public health importance, including *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Mycobacterium*

[37] http://erc.europa.eu/
[38] http://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/index_en.html

*tuberculosis*, *Candida* species, *Plasmodium falciparum* and HIV. Many of the projects focused on the development of new classes of antimicrobials and alternative strategies, and on the development of new diagnostic and susceptibility tests. Others investigated basic mechanisms of resistance, modes of transmission or novel intervention strategies in the hospital or the community, while yet others focused on preventing environmental pollution with antibiotics. An inventory of FP5 AMR projects was published[39].

The EU's commitment to AMR research continued in the 6th Framework Programme (FP6, 2002-2006), under which more than €186 million was awarded to projects for discovery and translational research activities. The discovery and development of novel antimicrobial drugs as well as identification of their molecular targets was a key funded research area. In addition, the development and spread of AMR was investigated together with novel evidence-based approaches to managing patients, with a view to optimising antibiotic use. An inventory of FP6 AMR projects was published[40].

In the 7th Framework Programme (FP7, 2007-2013), AMR is one of the key challenges within the Health theme. In addition, many basic research projects funded through the FP7-Ideas programme also address AMR. In total, around 75 projects on AMR are currently being funded by FP7 in diverse pathogens, with a total budget of around €273 million. These projects address the full scope of AMR, including bacterial, viral, protozoan and fungal infections of humans and animals, and have a variety of complementary aims, including the development of novel therapeutics, clinical trials to define the optimal use of existing antimicrobial drugs, the development of targeted diagnostics, and basic research on pathogens, understanding the mechanism of drug resistance and monitoring the spread of resistance. Another €33 million is foreseen for research projects that have been selected for funding in 2011 (9 projects are currently being negotiated). An inventory of FP7 AMR projects managed primarily as part of the Health theme has been published[41].

The amount of funds invested in AMR research has increased in successive framework programmes: €84 million, €187 million and €306 million in FP5, FP6 and FP7, respectively. The main areas of funding are therapeutics/antimicrobials, surveillance/monitoring/detection, prevention/control of spread, basic research and animal health. In addition, a small number of projects have investigated environmental effects and biosafety. The largest proportion of funding has been for therapeutics/antimicrobials. In FP5, this accounted for around half of total funding, while in FP6 and FP7 it was around 35-40%. Surveillance/monitoring/detection has represented around 20% of funds in FP5-FP7. Prevention/control of spread increased from around 6% in FP5 to 20% in FP6 and is currently around 13% in FP7. Basic research has increased from 15% of funds in FP5 and FP6 to around 22%. This increase is due to the establishment of the European Research Council in 2007, which primarily supports basic research.

The Directorate-General for Health and Consumer Protection (SANCO) also funds projects related to AMR, including European-wide surveillance projects of AMR, antibiotics prescription strategies, education measures and patient safety (see Appendix II).

FP6 also supports an ERA-NET project (PathoGenoMics)[42] for trans-European cooperation and coordination of genome sequencing and functional genomics of human-pathogenic

[39] Antimicrobial resistance research 1999-2002 (revised and extended edition), EUR 20495, European Commission (2003).
[40] http://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/pdf/fp6-projects-amrd_en.pdf
[41] http://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/pdf/eu-research-on-antimicrobial-resistance_en.pdf
[42] http://www.pathogenomics-era.net/

microorganisms. In the work programme of 2012, a call has been launched for a possible follow-up ERA-NET in the area of AMR.

The FAFB theme funds research both targeted at antimicrobials/AMR and at knowledge/control of animal diseases. There are diseases restricted to animals, and other ones transmissible between animals and humans: zoonoses. In addition, it aims at preventing and reducing human food-borne microbial infections by developing rapid detection methods for pathogens, innovative safe food processing, and packaging techniques and effective food safety management tools for the food industry. This contributes to decreasing the need to use antimicrobials and the related risk of transmission of AMR through the food chain and the environment to humans.

Under FP5 and FP6, a number of projects addressed the issue of how to find effective alternatives to address the removal from routine use of antimicrobials in animal feeds and the subsequent expected increased risk of health problems and decreased production. Over a dozen projects covered, in particular, diagnostics, use of chemical, bacterial and phage additives, or vaccines.

In animal health, focus was put on disease biology, epidemiology, gap analysis and prioritisation. It addressed diagnosis and control, either through management measures (including on-farm bio-security measures) or by improved therapeutics. Research was also supported on genomics of both animals and microorganisms in order to improve knowledge on host-microbe interactions and to open the way to genetic selection for disease resistance. Zoonoses were targeted, going from risk assessment to the basic phenomena of resistance of zoonotic agents.

Under FP7, basic animal sciences, including 'omics', are further strengthened and animal health is still a key challenge within the FAFB theme, covering viral, bacterial and parasitic diseases. Multi-factorial production pathologies (e.g. mastitis, health at weaning, PRRS) are also targeted, as well as zoonoses (e.g. control of *Campylobacter* at primary production).

FP7 also supports the ERA-NET project EMIDA[43] for trans-European cooperation and coordination of animal heath-related research. EMIDA launched two common calls, including the AMR theme. This ERA-NET is now being followed up through the ANIHWA ERA-NET that covers both animal health and animal welfare.

The FP7 Capacities – Infrastructure Programme supports several projects for the development of infrastructures that are important for combating AMR. The preparatory phase before implementation is being funded for ERINHA (European Research Infrastructure on Highly Pathogenic Agents)[44]: a project to build a pan-European research infrastructure aiming to reinforce the European coordination and capacities for the study and the surveillance of highly pathogenic microorganisms. A call was published in July 2011 for funding the preparatory phase before implementation for MIRRI (Microbial Resource Research Infrastructure)[45]: a project to build a pan-European distributed research infrastructure that provides microorganisms services facilitating access to high quality microorganisms, their derivatives and associated data for research, development and application. A complementary topic was also published in July 2011 for potentially funding an Integrating Activity on Biological Resources Centres for microorganisms. ERINHA and MIRRI have been included in the European Strategy Forum on Research Infrastructures (ESFRI) roadmap. An Integrating Activity project called NADIR (The Network of Animal Disease Infectiology Research Facilities)[46] is coming to an end. Its purpose is to facilitate

[43] http://www.emida-era.net/
[44] www.erinha.eu/
[45] www.mirri.org
[46] http://www.nadir-project.eu/nadir_project/

the development of Europe's high level bio-containment facilities. A topic was published in July 2011 for a potential continuation for experimental facilities for animal disease infectiology.

The Innovative Medicines Initiative (IMI)[47] is Europe's largest public-private partnership and aims to improve the drug development process by supporting efficient discovery and development of better and safer medicines for patients. With a €2 billion budget, IMI supports collaborative research projects and builds networks of industrial and academic experts in Europe that will boost innovation in healthcare. In March 2011, IMI announced 8 new projects that aim to boost drug innovation. One of those is RAPP-ID which, with a budget of nearly €15 million, aims to provide an integrated solution that addresses the technological challenges to enhance clinical decision-making on infectious diseases for improved clinical outcome and preservation of efficacy of antimicrobials. The project will develop a point-of-care test for rapid detection of bacteria, tuberculosis bacteria, fungi, as well as viruses and patients' markers of infection. The platforms will also determine resistance to the most commonly used antibiotics. Other topics in the area of AMR are under consideration for future calls.

### c) Related EU level initiatives

COST is an intergovernmental framework for European Cooperation in Science and Technology, allowing the coordination of nationally-funded research on a European level. The initiative of launching a COST Action comes from European researchers themselves (bottom up). The member countries participate on an 'à la carte' principle, in that only countries interested in the Action participate. COST plays a very important role in building the ERA, and anticipates and complements the activities of the EU Framework Programmes. Several COST actions focus on research in the area of AMR.

## *3. International Initiatives*

The emergence of AMR is a complex problem driven by many interconnected factors; single, isolated interventions have little impact. A global and national multi-sectorial response is urgently needed to combat the growing threat of AMR. This is fully recognised by the WHO that issued their Global Strategy for Containment of Antimicrobial Resistance in 2001. This document contains a series of supportive background materials and technical guidelines. AMR remains a priority for the WHO, as is apparent from their choice to select "combating antimicrobial resistance" as the theme for World Health Day 2011. On the occasion of this World Health Day, WHO stressed that further research is needed to guide efforts to combat AMR. It recognised that many factors contribute to the emergence and spread of resistance, but stated that there is still much to learn about the interplay between these factors and the cost-effectiveness of interventions to contain resistance.

At the EU-US summit in November 2009, AMR was one of the agenda items, and in the Summit Declaration, it was announced that the Commission with its US partners would initiate the setting up of a Trans-Atlantic Task Force on AMR (TATFAR), involving EU representatives (DG SANCO, DG RTD, ECDC, EMA, EFSA and the Trio Presidency), and US representatives from the relevant administrations (CDC, FDA and NIH). The objective was to identify areas where transatlantic collaboration would bring best added value. In 2010, the task force organised a series of public consultations and meetings to discuss and identify priority areas for further strengthened transatlantic cooperation on: (i) appropriate therapeutic use of antibacterial drugs in the medical and veterinary communities; (ii) prevention of drug-resistant infections; and (iii) strategies to improve the pipeline of new antibacterial drugs. Based on these consultations and the transatlantic dialogue, a draft report identifying 17 recommendations in the abovementioned fields has been prepared. This TATFAR report is awaiting endorsement by the EU and US leadership before

[47] http://www.imi.europa.eu/

publication. TATFAR has led to an improved EU-US collaboration on AMR and has resulted in the co-organisation of workshops (by NIH and DG RTD) on specific AMR topics (e.g. the EU-US workshop: "Challenges and solutions in the development of new diagnostic tests to combat antimicrobial resistance" planned to take place in Brussels on 28-29 September 2011).

AMR is a growing threat in Europe, but even more so in many other regions of the world. A global response will eventually have to be mobilised to meet this challenge. Europe has, mainly through Framework Programme support, built up a strong knowledge base in the field of AMR. This knowledge should be taken further towards extended international collaboration in specific areas where such collaboration would bring particular added value, similar to what is being done in the context of the TATFAR collaboration described above.

# V. Specific Objectives and Potential Outcomes

This JPI aims to remove classical barriers which inhibit European R&D cooperation and to facilitate the creation of a common knowledge base on the key issues related to AMR. Compatibility, exchange and comparisons of data will be achieved by establishing a common research-based approach to this grand societal challenge, by integrating relevant scientific fields across national borders, thus providing a major contribution to the creation of a common European research agenda with a shared common vision.

The initiative aims to develop and implement a common SRA concerning multidisciplinary science related to AMR, in order to help to safeguard the use of antimicrobials in the future. It will also provide new and better knowledge to support research and innovation, and help European, national and regional policy-makers develop the future policy mixes required to address the challenges posed by this increasing health threat.

Furthermore, joint programming and the establishment of a common European knowledge base on AMR-related research can also foster Europe’s economic competitiveness. By bringing together the best in AMR R&D, European developments and resulting innovations, products and services will be strengthened. This is not only crucial for a health system that heavily relies on effective antimicrobials, but will also be a major boost that is required to ensure that Europe remains at the forefront in the global effort to combat AMR. Furthermore, it will support the Commission's activities in this field, which will benefit from the knowledge created in this JPI and which can follow-up further research questions for the JPI to address.

In addition, the JPI should result in more efficient use of resources for research within participating Member States, and an optimised positioning of European and national research efforts.

Multiple research disciplines will be brought together as well as other stakeholders, such as policy-makers, industry, NGOs and patient representatives. Only such a combination will allow data to be provided for an evidence-based policy, which is a primary task and objective of this JPI.

The main focus will be on bacterial antibiotic resistance and human medicine, where both basic and applied research are of relevance. Veterinary medicine with relevance to humans should be included and no areas or pathogens should specifically be excluded at this time point. The Vision Document identifies the overall research needs which will be developed further in the SRA.

The overall and long-term objective is to combat the threat to human health posed by AMR. To achieve this objective within 5 years of the start of the initiative, the JPI aims to:

- **Identify new molecular markers**: Identifying useful markers will lead to useful tools, such as rapid diagnostics and potential targets for novel antibiotics. It is estimated that 40-80 new molecular markers could be identified within the scope of this JPI.

- **Identify novel lead molecules for antibiotic development**: There is a critical need for novel antibiotics, and this initiative will support the development of lead molecules up to Phase I clinical trials. The goal is to identify around 40-50 novel lead molecules.

- **Identify at least three novel alternative treatment methods**: These methods may be based on novel principles alone, combination of existing methods or combined use of old and new methods.

- **Refine prescription of antibiotics by developing diagnostic methods that, within hours, enable the identification of a sample bacterial strain and its susceptibility to antibiotic treatment**: Today it takes too much time to identify the infecting pathogen and its antibiotic susceptibility pattern, leading to the prescription of potentially ineffective antibiotics or antibiotics of a broad-spectrum type that increase the risk for resistance development and evolution.

- **Develop strategies for modelling of global epidemiology, risk assessment and disease burden of antimicrobial resistance**: This includes basic research on methodological tools for mathematical modelling of risk assessment, modelling of global spread of resistance and knowledge of the clinical and economic impact of AMR. Stakeholders from this and other initiatives will be invited to form a collaborative network to address issues such as data collection, quality control, interoperability and data access, need for analysis and modelling tools.

In addition to the vision paper, an SRA in the area of AMR will be drafted, aiming at indicating the research challenges and identifying scientific priorities based on societal needs and scientific evidence. The SAB will ensure the implementation of the SRA within a realistic timeline. The SRA will be compiled based on the Vision Document, the outcome of the workshop that took place on 2-3 May 2011, and the input from the SAB, that is being established.

# VI. Role of the European Commission in the JPI

The Commission may provide complementary measures for this JPI, which could include support for the management structure and establishment of the SRA, the provision of data, information and analysis on the state of play in this field in Member States and at EU level. Thus, the Commission will explore the scope for supporting cooperation on development of concepts and solutions, both at the national and EU level, promoting a holistic approach to AMR. Moreover, the JPI once operational will cooperate with the Commission for the implementation of research work, in particular with other initiatives in this field.