

The microbial challenge – An emerging threat to human health

A Joint Programming Initiative on Antimicrobial Resistance

The Lancet 2005:

About 70% of the bacteria causing serious blood infections in newborn babies in the developing world cannot be treated with the antibiotics recommended by the WHO.



*Will this be true also in
Europe?*

A Joint Programming Initiative
proposed by
Sweden and Italy

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¹ Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, 1 Goldmann DA. Hospital-acquired neonatal infections in developing countries. Lancet 2005; 365:1175-1188.

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 normally would have been fatal were now 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 receiving intensive care, organ transplants, cancer chemotherapy, and prenatal care.

However, the gains are now seriously jeopardised by the rapid emergence and global spread of microorganisms that are resistant to antimicrobials. We face an immediate risk that some of the most crucial tools in health care will soon become useless – a prospect that concerns everyone and could endanger the lives of future generations.

Antimicrobial resistance is an immense and truly global challenge, and the proposed Joint Programming Initiative (JPI) alone will not solve the problem. It will, however, be the starting point for the joint and coordinated research efforts required to address fundamental issues related to antimicrobial resistance.

1. Theme for the Joint Programming Initiative

Life-saving drugs are losing effectiveness

Infectious diseases are a potential risk to all of us. Alexander Fleming's Nobel Prize-winning discovery of penicillin, and the development of many new antibiotics, provided health care with important life-saving tools. Society indeed had reason for optimism; in 1967 the Surgeon General of the United States stated:

“The time has come to close the book on infectious diseases. We have basically wiped out infections in the US”.

(US Surgeon-General William H. Stewart, 1967)

Unfortunately, he has been proven wrong. The need for antibiotic therapy in modern health care will remain high and is anticipated to increase even further with an aging population and increased global infection rates. However, the increased use of antimicrobials – predominantly but not exclusively, antibiotics – will be accompanied by the development of antimicrobial resistance, i.e. the microorganisms causing life-threatening infections develop resistance to our drugs. This is an entirely natural and unavoidable process caused by pressure for environmental selection, essentially survival of the fittest, or in this case, survival of the most threatening microorganism. Fleming himself warned about the potential danger of using antibiotics when he received the Nobel Prize in 1945:

“The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

(Alexander Flemming, 1945)

Although health care has come to depend on the use of drugs to combat infectious microorganisms, the more frequently we use them, the less effective they will be in the long run. This is scarily illustrated by relating the outpatient use of antibiotics in different countries with, for instance, the percentage of penicillin-resistant pneumococci in the same countries (Figure 1).

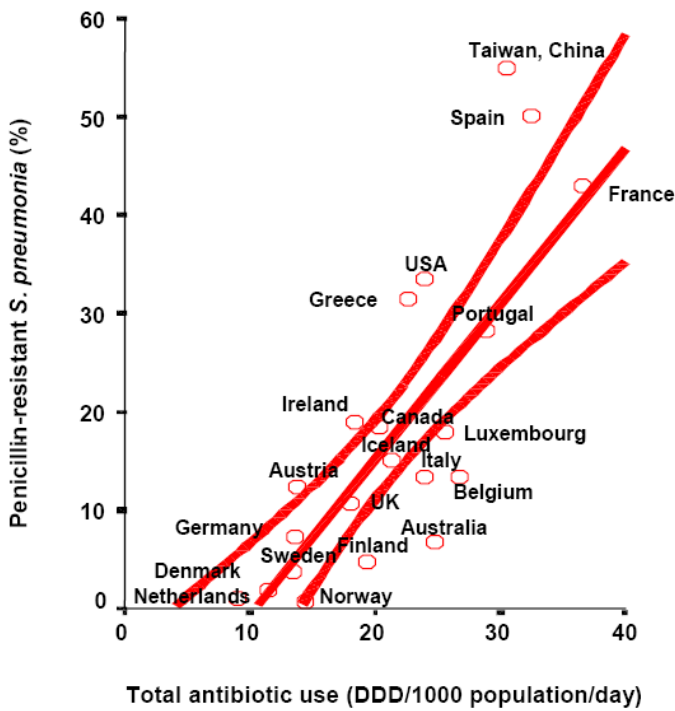


Figure 1. Relationship between penicillin-resistant pneumococci and outpatient antibiotic use (the 95% confidence interval is indicated). The correlation between the use of antibiotics and the development of resistance is obvious. In some countries, e.g. the Netherlands and Norway, resistance is very low whereas the USA and Taiwan, for example, have a much higher use of antibiotics and display considerable resistance. (DDD = daily defined dose)

From *Priority Medicines for Europe and the World* (2004); Kaplan W, Laing R. Geneva: World Health Organization (Source: Albrich WC et al., *Emerg Infect Dis* 2004).

The rate of resistance is also accelerating in countries that report relatively low usage of antibiotics, causing common organisms to become untreatable. For instance, within a decade the occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased dramatically in the United Kingdom, from less than 5% in blood culture isolates to more than 50% (Figure 2).

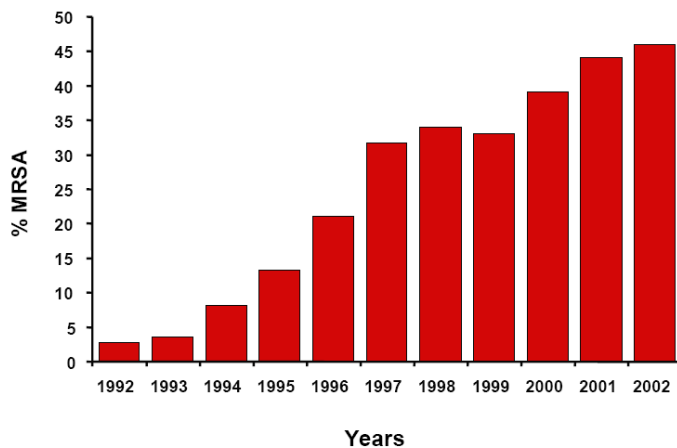


Figure 2. The frequency of MRSA in blood cultures with *Staphylococcus aureus*. England and Wales, 1992-2002.

From *Priority Medicines for Europe and the World* (2004); Kaplan W, Laing R. Geneva: World Health Organization (Source: Health Protection Agency, UK).

Major health threat

No longer is antimicrobial resistance simply a potential threat; it is a serious health problem and is accelerating rapidly. We witness today the results of decades of antibiotics misuse, and we have a responsibility towards coming generations to make up for 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 century¹. According to a recent report from ECDC and the European Medicines Agency (EMA), more than 25 000 patients die in the EU each year from infections caused by bacteria resistant to multiple antibiotics, so-called multidrug-resistant bacteria². 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 to premature death. Indeed, the report by ECDC/EMA estimated the overall direct costs to society in terms of extra healthcare costs and productivity losses total € 1.5 billion each year. However, the indirect costs to European countries are likely to be several-fold this amount³.

In several European countries, resistance rates to a single antibiotic exceed 50%, and resistance to multiple antibiotics is a common and increasing problem. It should be emphasised that antimicrobial resistance is not something that concerns only sick people and patients. In fact, 60% to 70% of healthy people are estimated to 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 antimicrobial resistance can affect every European citizen, and no one is exempt.

Antimicrobial resistance in animals

It is also important to emphasise that the problem of antimicrobial resistance is far from confined to humans and the healthcare system. The use of antibiotics in animals, particularly for the purpose of meat production, causes selection of resistant bacteria that can then spread to humans through food consumption, the environment, or close contact with animals. In the EU, the use of antibiotics as growth promoters has been banned. There is evidence that this action has led to a lower prevalence of antimicrobial resistance in some animal bacterial populations. However, emerging data also demonstrate a rapid rise in bacteria resistant towards antibiotics of the beta-lactam type, especially in the poultry industry. It is safe to conclude that, just as in human populations, the excessive use of antibiotics in animals increases the risk of developing resistance⁴.

¹ Priority Medicines for Europe and the World (2004). Kaplan W, Laing R. Geneva: World Health Organization.

² The bacterial challenge: time to ReAct. ReAct/ECDC/EMA joint technical report. European Centre for Disease Prevention and Control (2009).

³ Conference report; Innovative Incentives for Effective Antibacterials (2009)

⁴ Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections. EFSA Journal 2009; 7(11):1372

Global health threat

The global impact of the antimicrobial resistance problem cannot be over-emphasised. Dynamics of human populations – particularly in the past 25 years – have contributed significantly to the rapid spread of several multidrug-resistant infectious microorganisms. Given the speed and global reach of the spread we can reasonably characterise it as a pandemic rather than an epidemic⁵. An illustration of this is the spread of the 23F clone of penicillin resistant pneumococci. Although first reported in Europe, it was soon found in Argentina, Brazil, Chile, Taiwan, Columbia, Malaysia, Mexico, the Philippines, Republic of Korea, South Africa, Thailand, USA, and Uruguay⁶ (Figure 3).



Figure 3. Spread of the 23F clone of penicillin resistant pneumococci from Europe to countries across the world.

Human activities promote faster and further spread^{7,8} of resistance genes. Airlines, for instance, transport more than two billion passengers annually. Other factors that increase the spread of resistant pathogens include poor hygiene, worldwide distribution of food, and erratic use of antibiotics in hospitals and the community^{9,10}. Consequently, we must also consider the antibiotic resistance levels in countries outside of Europe. In developing countries, contaminated water supplies, close contact between farm animals and humans, unregulated antibiotic usage in husbandry, and the high level of non-prescribed use of antibiotics join to create an ideal environment for rapid, unchecked dissemination of antibiotic resistance. This emphasises the importance of non-European countries as potential sources of antibiotic resistance that easily can spread to Europe. An illustration would be the very first description of a specific carbapenem-resistant strain of *Klebsiella pneumoniae* in Sweden in 2008. This antimicrobial resistant bacterial strain originated in New Delhi, India where the patient had acquired a urinary tract infection before travelling to Sweden. This type of resistance (NDM-1) is now widespread in the UK (mainly through Indian contacts) and has spread to five other European countries in less than 2 years.

⁵ The CTX-M β -lactamase pandemic. Cantón R, Coque TM *Current Opinion in Microbiology* 2006, 9:466-475.

⁶ Bulletin of the World Health Organization 2002, 80:126-133.

⁷ Emergence and resurgence of meticillin-resistant *Staphylococcus aureus* as a public-health threat. Grundmann H et al. *Lancet* 2006, 368:874-885.

⁸ Report on infectious diseases 2000: overcoming antimicrobial resistance. WHO 2000.

⁹ World health report 2007: a safer future: global public health security in the 21st century. WHO 2007.

¹⁰ The clonal spread of multidrug-resistant nontyphi *Salmonella* serotypes. Butaye P et al. *Microb. Infect.* 2006, 8:1891-

We have no way to stop the global spread of resistant microorganisms. Even at places as remote as the Arctic Ocean, birds have been shown to carry antimicrobial drug resistance strains¹¹. Thus, resistance genes can be found even in regions where no selection pressure for resistance development exists. Regardless of the measures we take in Europe to combat antimicrobial resistance, we must realise they will have a limited long-term impact unless we also contribute to the situation in developing countries.

Given Europe's extensive interactions with non-European countries – but countries that nonetheless impact on European antimicrobial resistance rates – this initiative will have a global impact on tackling the pressing problem of antimicrobial resistance.

Innovations and industry

For many years the pharmaceutical industry met society's need for antibacterial drugs. The situation is now completely different as existing antibiotics are losing their effect at an alarming pace while the development of new antibiotics is declining. From the 1930s through the 1960s more than a dozen new classes of antibiotics were developed. Since then, only two new classes have been developed¹².

Investments in research and product development to address the problem are diminishing. Part of the explanation lies in the fact that, from a commercial standpoint, an ideal drug is one used by many patients for lifelong treatment. An effective antibiotic compound, however, should be used restrictively and for only a few days. Hence, from a business standpoint antimicrobial compounds may not have all the traits usually associated with a “successful drug”. The unmet medical need is nevertheless obvious, and considerable effort and cost have been expended in this area to address the need. However, development of new antibiotics has turned out to be difficult, even with the advent of large-scale genomic projects, and success has been limited. Accordingly, “Big Pharma” seems to be withdrawing from the antimicrobial field. The Medtrack database indicates that fewer than 50 small- and medium-sized enterprises conduct research on antimicrobial lead compounds. Since the number of companies in this research field is limited, the expected outcome in terms of new drugs with new mechanisms of action is insufficient.

Developing a drug, taking it from an identified biological mechanism to the market, is extremely costly, and the fact that many fail during the process adds to the cost. The pharmaceutical industry has limited resources for basic science, and their organisations are incapable of generating the large number of basic research findings necessary to feed the pipeline. On the other hand, industry may be strong in high-throughput screening, chemical libraries, and have other large-scale advantages.

By supporting basic research on resistance development and spread, the Joint Programming Initiative could increase the number of identified potential drug targets and novel drug mechanisms. European Joint Programming in the field of antimicrobial resistance would offer an excellent framework for promoting the research efforts required to provide new drugs.

¹¹ Dissemination of multidrug-resistant bacteria into the Arctic. Sjölund M et al. *Emerg. Infect. Dis.* 2008, 14:70-72

¹² Bad bugs, no drugs: as antibiotic discovery stagnate and a public health crisis brews. Infectious Diseases Society of America July 2004. www.idsociety.org/badbugsnodrugs.html

Why joint programming in this area?

The Council of the European Union stated on 1 December 2009, in its *Council Conclusions on innovative incentives for effective antibiotics*¹³, that it:

“Calls upon the Member States and the Commission to support the sharing of research infrastructure, recruitment of researchers, stimulation and support of global research cooperation, increasing spread of research results and knowledge through exchange structures and considering existing and new financial instruments.”

(Council of the European Union, 2009)

The Council Conclusions were adopted by 27 Ministers of Health in Europe. The proposed Joint Programming Initiative is well in line with the actions suggested in the Council Conclusions. The work programmes and research activities to be based on this proposal will not only address urgent scientific and clinical issues, but also contribute to European leadership in the battle against antimicrobial resistance.

EU funding currently accounts for only ~5% of all European research financing, and national organisations provide the great majority of funding. However, while many of these organisations allocate funding to research projects on antimicrobial resistance through open, competitive grants, few have a defined programme or strategy for research in the field, or participate in international networks or collaborations dedicated to the problem (see Appendix I for details). Hence, it is obvious that research on antimicrobial resistance in Europe is scattered, and a focused, large-scale approach involving the combined efforts of many countries is essential to address specific current medical needs and future emergence of new resistant pathogens. Action is needed on many fronts; new approaches to prevent and treat infections, innovations into new drugs and diagnostic tools, better molecular surveillance, a better understanding of how pathogens recruit resistance genes, and models for predicting resistance to antibiotics.

A European Joint Programming Initiative targeted at this area has a high potential to boost research advances and innovations and to increase the competitiveness of the European Union on a global scale. Europe has many of the world’s leading scientists on antimicrobial resistance. They are universally respected, and therefore such an initiative will provide a consorted, holistic approach to tackle antimicrobial resistance, bringing together world experts and providing unique synergy on topics that require further action and investment.

Whilst other European initiatives and funding opportunities exist, this JPI proposal encapsulates the broader aspects of antimicrobial resistance and provides a longitudinal, holistic, and overarching approach that is currently lacking in Europe. The proposed activities will mobilise the available national resources of several nations in an optimal way, while ensuring minimum duplication of effort, utilise existing expert groups, and synthesise holistic activities to make Europe a world leader in research on antimicrobial resistance.

¹³ Council of the European Union. Council Conclusions on innovative incentives for effective antibiotics. Adopted at 2980th Employment, social policy, health and consumer affairs council meeting in Brussels, 1 December 2009.

2. **Proposing GPC member/members**

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3. **Objectives**

The global and multifaceted problem of antimicrobial resistance will demand vast and versatile solutions. A comprehensive solution to the problem requires measures from many sectors of society; policy makers, health care, education, industry, environmental agencies, agriculture, veterinary medicine, research, and other areas. The Joint Programming Initiative cannot address all aspects of the problem, but may show a way forward by producing new research and creating networks that can create long-term momentum for other areas in society.

The overall and long-term objective is to combat antimicrobial resistance threatening human health.

To achieve this objective within 5 years of the start, the Joint Programming Initiative aims to:

- *Identify new molecular markers*

Identifying useful markers will lead to useful tools, such as rapid diagnostics and potential targets for novel antibiotics through in-silico modelling. We estimate 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-1 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, combinations of existing methods, or combined use of new and old 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.*

For most bacterial infections, it takes several days to identify the pathogen and its antibiotic susceptibility pattern. By that time, often the patient has already been prescribed antibiotics that might potentially be ineffective, or are a broad-spectrum type that increases the risk for resistance 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 antimicrobial resistance. 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.

4. **Research questions being addressed**

The proposal outlines a research programme on antimicrobial resistance. As the most urgent clinical problems concern bacterial resistance, this will be the primary focus of the work. However, antimicrobial resistance is by no means limited to bacteria – it is a phenomenon that applies also to other microorganisms: fungi, viruses, and parasites. These will also be addressed when appropriate, although this is not stated in detail at this stage of the initiative. The overall objective is to combat antimicrobial resistance threatening human health. However, we do not live in isolation and therefore we will also address antimicrobial resistance development in animals that represent a potential risk for human health.

The proposed work, outlined as three major blocks or themes (Figure 4), will be transformed into a complete set of work packages if the Joint Programming Initiative is accepted. This process will involve the active participation of a JPI Scientific Advisory Board to ensure that all aspects of the programme are of highest clinical and scientific quality.

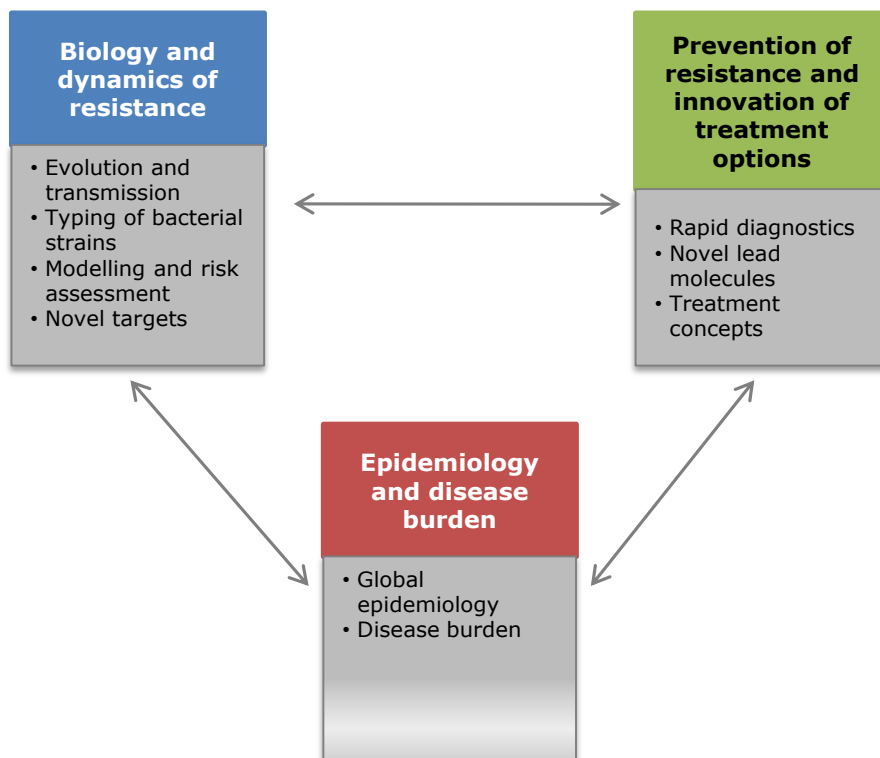


Figure 4. Outline of research questions being addressed.

Biology and dynamics of resistance

The aim is to understand the underlying biology of those factors most important in influencing the emergence and spread of resistant infectious microorganisms within and between humans as well as from animals and the environment.

The following research areas will be explored:

- ***Evolution and transmission:***

An understanding of how bacteria evolve to withstand and/or evade the action of currently available antibiotics is crucial knowledge for devising new strategies to minimise resistance evolution and for designing new drugs. This research area suggests identifying bacterial mechanisms and factors that are important for antimicrobial resistance evolution, including the role of plasmids and other genetic elements in the dissemination of antimicrobial resistance. A particularly important issue to understand is why some bacteria are especially prone to transmission and global dissemination, while others remain locally confined. A better understanding of these issues will enable more-refined strategic designs for therapy and prevention.

- ***Typing of bacterial strains:***

This area aims to develop and optimise techniques for typing of bacterial strains. Typing techniques are used in different epidemiological applications, e.g. confirming linkage in outbreak investigations and describing the distribution of bacterial types. The choice of typing technique is essential for increasing our understanding of the pathogenesis and transmission, and eventual disease prevention.

- ***Modelling and risk assessment:***

There is a need for conceptual and quantitative methodological tools to allow prediction of when, where, and how resistance will develop when antibiotic pressures are applied. This research area aims to provide the experimental knowledge required to mathematically model and perform risk assessments concerning the development and spread of antimicrobial resistance in humans, animals, and the external environment.

- ***Novel targets:***

A deeper understanding of the mechanisms by which bacteria gain resistance to antibiotics will aid in identifying novel targets of drugs or treatment. In the subsequent selection of drugs and treatments, the probability of rapid resistance evolution will be an important criterion.

Prevention of resistance and innovation of treatment options

The primary aim is to reduce the need for antibiotics through disease prevention, refined treatments, alternative treatments, and rapid diagnostics of pathogens and resistance patterns.

Research areas include:

- ***Rapid diagnostics:***

This research area aims to provide the knowledge base necessary for developing tools for rapid diagnostics of bacterial, fungal, and other infectious microorganisms and their antimicrobial resistance pattern. For most bacterial infections, identification of the pathogen and its antibiotic susceptibility pattern requires several days, and by that time often the patient has already been prescribed antibiotics that might potentially be ineffective. Clinical signs and symptoms of fungal infections are often non-specific and difficult to distinguish from those seen with bacterial infections. This leads to many cases of inappropriate treatment and subsequently contributes to the emergence and spread of antimicrobial resistance by generating unnecessary selective pressures. Hence, to avoid inappropriate treatment and reduce antibiotic misuse we need diagnostic methods that can provide rapid and accurate information. If successful, these diagnostic tools can be predicted to generate widespread use, thereby attracting commercial interests for further development and marketing.

- ***Novel lead molecules:***

Antibiotics have been the “workhorses” in antimicrobial treatment and are of immense importance to society. For every successful new drug, several promising novel lead molecules need to be identified. This can be done within the JPI. Subsequently, lead molecules can be evaluated within the JPI, SMEs (small- and medium-sized enterprises), or pharmaceutical companies. Research aimed at novel lead molecules will include improved tools for predicting toxicology, predictive tools for developing novel antimicrobial drugs, and screening natural products to identify novel scaffolds for further development.

- ***Treatment concepts:***

Since resistance to antibiotics inevitably builds over time, it is also highly important to expand the choice of treatment alternatives available to healthcare providers by broadening our arsenal against pathogens. Several routes of research aimed at new treatments include methods such as antimicrobial peptides, therapeutic antibodies, and vaccines. Other routes include strategies such as bacteriophages (bacteria-specific viruses that kill bacteria) and antivirulence strategies to disarm bacteria. The lifespan of current antibiotics may be prolonged through the use of potentiators of antibiotics, or through well-executed studies of refined use of antibiotics. In studies of refined use, the combined use of two or more antibiotics should be explored as well as dosage optimisation and shortened treatment times to minimise selection of resistance in the normal bacterial flora.

Epidemiology and disease burden

The aim is to increase knowledge of the global prevalence and spread of different infectious microorganisms and to estimate the financial and societal burden of disease. The following research areas will be addressed:

- ***Global epidemiology:***

The number of infections caused by resistant microorganisms continues to increase in the EU and worldwide. Mobility of people between countries and continents enables resistant bacteria from other parts of the world to reach and infect EU citizens. Hence, it is not enough to investigate the prevalence and spread of resistant bacteria in Europe. To design strategies towards fighting resistance development, and to identify the most important drugs to have in the pipeline, it is crucial to understand the situation worldwide. This includes knowledge of the veterinary use of antibiotics and the prevalence of antimicrobial resistance in the food and agriculture industry. Global epidemiological studies are currently lacking, and vast efforts are needed to organise data collection, an integrated information infrastructure, and mathematical modelling of large-scale data. This JPI suggests designing a framework that brings together current programmes and collaborates with existing agencies in an initiative on global epidemiological research of antimicrobial resistance. However, fully implementing such a programme would be too elaborate for the scope of this JPI. The programme will be initiated by the JPI, but needs to be implemented by several bodies.

- ***Disease burden:***

Clearly, infections caused by resistant microbes lead to suffering, incapacity, and death and impose an enormous financial burden on healthcare systems and society in general. However, detailed figures on the direct costs of prolonged illness and treatment in hospital, the indirect costs of lost productivity, and the societal costs from morbidity and mortality are lacking, leaving us to rely on estimates and extrapolations from smaller studies. Knowledge of the clinical and economic impact of antimicrobial resistance is essential to influence programmes and behaviour in healthcare facilities, to guide policy makers and funding agencies, to define the prognosis of individual patients, and to stimulate interest in developing new antimicrobial agents and therapies.

5. ***Added-value, benefits and impact***

- ***Sharing the burden***

The increasing resistance of bacteria against 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.

- ***Joining forces***

Currently, most research initiatives in this field are at a national level. A joint European approach has the potential to maximise the effectiveness of these efforts, to reduce redundancy, and to utilise resources more efficiently. The critical mass of excellence needed to act on the current scientific challenges can be achieved only by reinforcing research integration through transnational initiatives.

- ***Providing a stronger research base***

The problem of antimicrobial resistance is being addressed by several international organisations, including the World Health Organization (WHO), the European Centre for Disease Prevention and Control (ECDC), ReAct (Action on Antibiotic Resistance), European Medicines Agency (EMA), and EARSS (European Antimicrobial Resistance Surveillance System). Although these organisations make important contributions to the field, they do not provide the *long-term funding* commitments required to solve the major research questions. Therefore, the Joint Programming Initiative will ensure long-term funding and serve to complement other initiatives, creating momentum with the potential to move the frontiers forward and offer new opportunities for industry, new tools for society and policy makers, and inspire other necessary initiatives.

- ***Collaboration with existing research initiatives***

The only existing multinational research collaboration involving antimicrobial resistance appears to be ERA-NET PathoGenoMics. The primary focus of PathoGenoMics is genome research on human-pathogenic microorganisms. Of the 25 consortia funded in the first two joint calls for proposals, only a few of the project descriptions explicitly addressed the problem of antimicrobial resistance. Nevertheless, the ERA-NET PathoGenoMics has established a valuable basis for transnational activities in the field of antimicrobial resistance. Close collaboration is planned between the Joint Programming Initiative and ERA-NET PathoGenoMics – and other relevant European initiatives – to further strengthen the coordination of research activities and to assure minimum duplication of effort.

- ***Sharing knowledge***

Levels of research infrastructure and available funding vary widely among the 27 Member States. It is also apparent that not all countries can cover all aspects of the research and clinical efforts required to combat antimicrobial resistance. A Joint Programming Initiative would enable all Member States to participate in projects and gain direct access to new knowledge.

- ***Contributing to the European Research Area***

A Joint Programming Initiative will strengthen the structures of information exchange

within the community. It will promote mobility of students and faculty. It will facilitate establishing and providing access to larger study populations than otherwise possible in most national initiatives. It will aid communication and integration of resources from a global perspective, e.g. in collaboration with the United States, Asia, and developing countries, at a time when several processes are targeting EU's role as an actor on trans-Atlantic and global levels.

- ***Facilitating drug development***

Regardless of what can be done to address antimicrobial resistance, the world needs new drugs. The proposed Joint Programming Initiative will coordinate and promote research fundamental to the further development of drugs.

6. *Preliminary suggestions concerning the governance and implementation of the JPI*

Governance

For a European strategy for research programming on antimicrobial resistance to be successful it need to involve stakeholders from science, health care, and industry. Representatives of these areas should thus be involved at different levels to reach a full scope of national-, European-, and global-level options in performing and funding research activities.

The management structure will adhere to possible guidelines given by the High Level Group for Joint Programming, and should include:

- a. Management Board
- b. Executive Board
- c. Scientific Advisory Board
- d. Secretariat

Management Board

Any Member State or State associated with the European Framework Programme willing to participate in the JPI on Antimicrobial Resistance may be represented on the management board. Each participating State may appoint a maximum of two representatives, who should have a government mandate. The management board elects a JPI Director, who chairs the meetings and represents the JPI in all external contacts.

The management board will decide on:

- a shared vision concerning the nature of the challenge
- the objectives of the initiative
- the Strategic Research Agenda

The management board will identify the research issues, the public research instruments, and the priorities for joint action, taking into account already existing national, EU, and global activities. Furthermore, the management board will decide on the possible implementation of working groups that would serve as operational units and consist of national and/or regional funding bodies from the contributing Member States. It will also supervise handling of intellectual properties rights (IPR).

The management board will report to the political level of the participating States, GPC, and

CREST on the progress on the JPI. It will also communicate with other initiatives and programmes, e.g. WHO, ECDC, EARSS, IMI (Innovative Medicines Initiative), Programme Management Committees of the Specific Programme Cooperation Configuration Health, Programme Management Committees of the Specific Programme Capacity Research Infrastructure, and ERA-net Pathogenomics.

Executive Board

If more than 10 countries participate in the JPI on Antimicrobial Resistance an executive board will be established from among the members of the management board. The executive board, chaired by the JPI Director, will assist the management board in preparing meetings and proposals, thereby allowing the management board to focus on strategic decisions. The executive board will ensure implementation of decisions and monitor follow-up of the actions. Furthermore, the executive board will coordinate the activities of the other administrative and governing bodies of the JPI, foresight activities, programme research activities (calls for proposals), assessment of JPI impact, training activities, dissemination of results, etc.

Scientific Advisory Board

The scientific advisory board will assist the management board in establishing a Strategic Research Agenda and propose scientific priorities based on societal needs and scientific evidence.

The functions of the scientific advisory board will include:

- input to the Strategic Research Agenda
- suggestions of prioritisation in ranking the order of each research area
- strategic advice to the management board on selecting areas for joint calls
- recommendations on implementing the final Strategic Research Agenda.

Members of the scientific advisory board shall be selected from among the most pre-eminent scientists in the field. The composition of the scientific advisory board shall reflect:

- recognised leadership in relevant fields
- understanding of the organisational and operational setting of transnational cooperation
- experience in programmatic procedures and implementation of strategic research
- experience in health quality management.

Secretariat

A secretariat will support the management structure and the JPI Director and will provide professional administrative and organisational support. The functions of the secretariat will include:

- assisting the management board, JPI Director, executive board, and scientific advisory board to organise meetings and prepare documents and reports
- ensuring logistical coordination and communication among different bodies of the management structure and other relevant bodies
- preparing the necessary budgetary arrangements to operate the management structure
- maintaining an internal web page (intranet) for providing easy access to internal documents, information and results
- maintaining an external web page directed towards the scientific and medical community
- assisting with dissemination activities.

Intellectual Property Rights

One objective of the proposed Joint Programming Initiative is to provide a mechanism or process for identifying new drug candidates that can be further developed by the pharmaceutical industry. Hence, high priority must be given to resolving issues related to intellectual property rights (IPR). IPR issues will be discussed during the implementation phase and then continuously monitored.

Implementation

If the High Level Group for Joint Programming accepts the present proposal at its meeting on 4 May 2010, a pre-implementation phase of the JPI will be initiated immediately. Following a final decision by the Competitiveness Council later in 2010, the main implementation phase will commence.

Pre-implementation phase (May – prel. December 2010)

The present JPI proposal is only an outline of the work and structures needed to address *The Microbial Challenge* and it is thus urgent to develop this into a real work programme. The preparatory work for this will start during the pre-implementation phase with the aim of:

- establishing a temporary Implementation Group
- establishing a temporary secretariat to support the implementation activities
- identifying Member States interested in participating in the JPI
- identifying stakeholders
- identifying key individuals as candidates for the Scientific Advisory Board and as JPI Director
- preparing on plan and time table for the procedures towards setting up workpackages etc

A JPI Pre-Implementation Meeting will be organised in September (prel.; possibly in connection to the conference *The global Need for Effective Antibiotics – Moving Towards Concerted Action.*, which is organised, with support of the Swedish government, in Sweden 6-8 Sept.). A work group appointed at this meeting will be responsible for further activities.

Implementation phase (prel. January – June 2011)

The objective of the implementation phase is to establish the full governance structure, provide a draft of a work programme (including work packages, deliverables and milestones) based on the proposed Research Questions, and to begin financial considerations.

Appendix I

Several national funding agencies in Europe were consulted to gain an overview of the current status of antimicrobial resistance research. We must stress that a comprehensive inventory of existing research was beyond the scope of this proposal, and we cannot exclude the possibility that some initiatives or programmes were not detected in our analysis. The funding agencies consulted were asked the following three questions:

1. *Does your organisation finance any programmes and/or larger projects within the field of antimicrobial resistance?*
2. *Does your organisation participate in any national and/or international collaborations – with other research financiers, with organisations – such as the EC and WHO, or with industry – within the field of antimicrobial resistance?*
3. *Does your organisation have a defined research strategy for antimicrobial resistance? If so, could you please provide a brief summary of the strategy.*

Most of the national financing organisations consulted allocate funding to research projects on antimicrobial resistance through open, competitive grants. However, few of the organisations stated that they participate in any international networks or collaborations dedicated to the problem of antimicrobial resistance (AMR), or that they have a defined research strategy for AMR. Major initiatives specifically dedicated to the problem of antimicrobial resistance were identified in the Netherlands and in the United Kingdom. The Dutch Organisation for Health Research and Development (ZonMw) recently opened a comprehensive research programme called *Priority Medicines Antimicrobial Resistance*, which will fund basic and applied research totalling 14.8 million Euros over a 9-year period (2009-2018). In the UK, the Medical Research Council (MRC) has joined with Canada to launch a call for proposals in the area of antibiotic resistance. In addition, the MRC has also issued a joint call with Singapore on infectious diseases, although this is not solely dedicated to research on AMR. Until last year, when financing was cut, the Latvian Council of Sciences funded a research programme in the field of antimicrobial resistance – entailing participation in international networks such as EARSS and ESAC.

Within the framework programmes, research projects addressing antimicrobial resistance have received EU funding since 1999. Within FP7, the budget spent so far on research projects in the field is €100 million. Table A1 lists the research projects currently supported.

Project Acronym	Project Name	EC Contribution	Starting Date	Duration	Co-ordinated from
AEROPATH	Identification, characterisation, and exploitation of novel Gram-negative drug targets	€ 4 591 463	1/11/2008	48 months	UK
AntiPathoGN	Identification and validation of novel drug targets in Gram-negative bacteria by global search: a trans-system approach	€ 5 943 961	1/01/2009	48 months	CAT
ANTIRESDEV	The effects of antibiotic administration on the emergence and persistence of antibiotic-resistant bacteria in humans and on the composition of the indigenous microbiotas at various body sites	€ 5 368 088	01/11/2009	36 months	UK
CAREPNEUMO	Combating Antibiotics Resistant Pneumococci by Novel Strategies Based on in vivo and in vitro Host-Pathogen Interactions	€ 2 999 999	01/03/2009	36 months	DE
CONCORD	CONtrol of COmmunity-acquired MRSA: Rationale and Development of counteractions	€ 2 994 192	01/11/2008	36 months	NL
DIVINOCELL	Exploiting Gram-negative cell division targets in the test tube to obtain antimicrobial compounds	€ 5 956 086	2009	48 months	ES
HYPERDIFF	The Physiological Basis of Hypervirulence in Clostridium difficile: a Prerequisite for Effective Infection Control	€ 2 992 181	1/11/2008	36 months	UK
NABATIVI	Novel Approaches to Bacterial Target Identification, Validation and Inhibition	€ 5 506 000	1/01/2009	48 months	IT
PAR	Predicting antibiotic resistance	€ 6 000 000	January 2010	36 months	SE
PILGRIM	Preventing community and nosocomial spread and Infection with MRSA ST 398 - instruments for accelerated control and integrated risk management of antimicrobial resistance	€ 2 993 728	01/01/2009	36 months	UK
PNEUMOPATH	A comprehensive dissection of pneumococcal-host interactions	€ 2 999 843	1/01/2009	36 months	UK
SATURN	Impact of Specific Antibiotic Therapies on the prevalence of hUman host ResistaNt bacteria	€ 5 999 436	01/01/2010	60 months	CH
SYBARIS	Finding biomarkers of antimicrobial drug resistance via a systems biology analysis of fungal pathogen interactions with the human immune system	€ 4 291 161	2010	36 months	UK
TEMPOtest	An Integrated Tool-Kit for the Clinical Evaluation of Microbial Detection and Antibiotic Susceptibility Point-of-Care Testing Technologies	€ 3 064 573	18/01/2010	36 months	NL
TROCAR	Translation Research On Combating Antimicrobial Resistance	€ 2 999 445	02/01/2008	36 months	ES

Table A1 List of current FP7 projects in the field of antimicrobial drug resistance.