Joint Programming Initiative on Antimicrobial Resistance: An emerging threat to human health

Vision Document

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Foreword

Antimicrobials have saved the lives and eased the suffering of millions of people. However, antimicrobial resistance and its global spread threaten the continued effectiveness of many medicines used today to treat the sick, while at the same time it risks jeopardizing important advances being made against major infectious killers.

Antimicrobial and, more specifically, antibiotic resistance is a growing, global health problem whose extent we have not been able to stop. Regardless of the national-level measures taken in Europe to combat this threat, the beneficial effect of antibiotic use restriction will be evident only in the long term. Furthermore, we must realize it will have a limited impact unless we also contribute to the situation in other countries, particularly in developing countries.

No longer is antimicrobial resistance simply a potential threat; it is a serious health problem and it 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. Resistance is a problem that goes beyond humans and the healthcare sector; therefore it is important to involve all implicated sectors.

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 and societal efforts required to address fundamental issues related to antimicrobial resistance and host-pathogen interaction.

1. Description of the problem

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.

Any bacterium can become resistant to one or several classes of antibiotics (multiple drug-resistant bacteria: MDR bacteria and, occasionally, pan-resistant bacteria). The slow process of emerging resistance over the years has led to a competition between the establishment of different resistances and the development of new antibiotics to combat these resistances. While it was easy to react towards one type of resistance (against one class or subclass), the progressive addition of resistances in different species has resulted in some therapeutic deadlocks. In other words, the industry and by consequence society today has almost lost the battle against resistant bacteria.

Several examples can be mentioned. After the introduction of penicillin it was obvious that penicillin resistance previously existed in part of the population of *Staphylococcus aureus* due to the presence of a beta-lactam destroying enzyme (penicillinase). As soon as methicillin was introduced, to combat these penicillin-resistant *S. aureus,* the emergence of methicillin-resistant *S. aureus* (MRSA) was described in hospitals in different countries. It was very promptly recognised that the major problem of these resistant strains was their capacity to disseminate to other patients through hand carriage and other health care procedures. In many countries, it took time (years) to take consciousness of the phenomena and to set up costly processes to try to handle the problem. The same problem could be described for all resistances in all species and is now enhanced by the fact that the dissemination process is increased by the facilitated exchanges due to the international travel. Unfortunately In the community, the problem of resistance is also rising slowly for many species but precise data are lacking since resistance is often reported only for hospitals

The rate of resistance is also accelerating in countries that report relatively low usage of antibiotics, causing common organisms to become untreatable. Along the years most of the important pathogens involved in infections have become multi-resistant to different extents. MDR bacteria are now present not only in the hospital but also in the community and have drastically changed the approach of empiric therapy. Prescription of antibiotics will either lead to the prescription of the most recent antibiotics or to an increase of the daily dose, which in turn favours the emergence of new resistances and the dissemination of existing ones. It should be emphasized that the emergence of MDR bacteria is a worldwide problem and that many factors have contributed to their dissemination.

Known causes of the problem from the biological and clinical point of view

Today the resistance has become a worldwide problem and an increasing threat. Among the different nations, according to their antibiotic policy, the type of the prescription control, the maturity of their health policy, the type of resistance and the magnitude of its emergence may have varied over time but no one escapes from the problem.

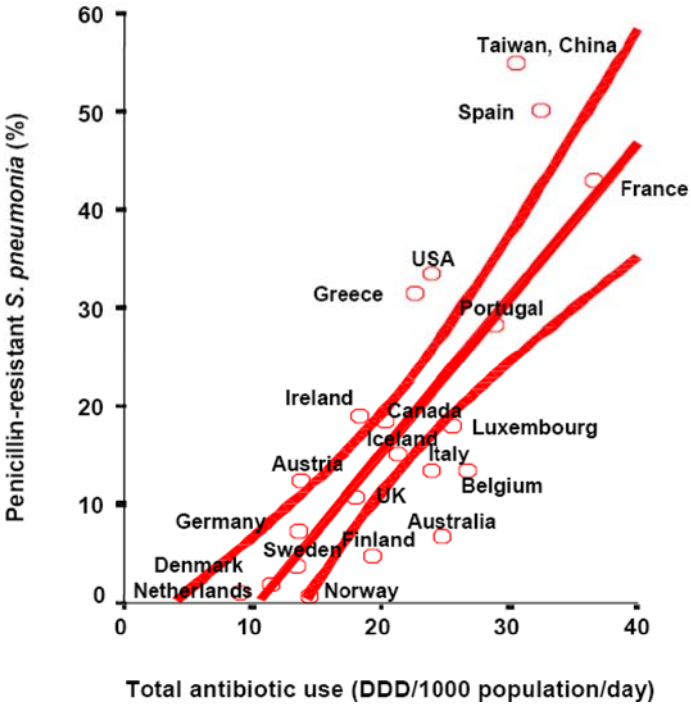


Figure 1. Relationship between penicillin-resistant pneumococci and outpatient antibiotic use (the 95% confidence interval is indicated). The correlation between the use of antibiotics and the development of resistance is obvious. In some countries, e.g. the Netherlands and Norway, resistance is very 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).

Fundamental research has made real progress in the understanding of the mechanisms of resistance to antibiotics. Thousands of articles have been published along the years as new antibiotic resistance mechanisms emerge in parallel with the introduction of novel antibiotics. This has been sustained by the broad progress in molecular biology, biochemistry, and structural studies. A recent database lists the existence of more than 20,000 potential resistance genes (r genes) of nearly 400 different types, predicted in the main species from available bacterial genome sequences (Origins and Evolution of Antibiotic Resistance. Julian Davies* and Dorothy Davies MMBR 2010 74 417-433).

The origin of resistance can be divided in two main categories. One is the direct selection of the resistance by mutation of a chromosomal gene. The other is the acquisition of already exiting genes most frequently present in other species which are not known to be main pathogens for humans. These species can be present in the environment, the animals or in the commensal flora of the human gut where numerous species (X100) are present. (Origins and Evolution of Antibiotic Resistance Julian Davies* and Dorothy Davies MMBR 2010 14 417-433). Resistance determinants to all antibiotics could be found easily in different soil organisms. Under the selective pressure of antibiotic they may well be introduced in human pathogens or the commensal flora becoming a major issue in terms of dissemination.

For many of these resistance mechanisms, biochemical and structural studies would aid the understanding of the structural changes which result in the inefficacy of the drug. The same structural studies can be applied to find derived molecules which could evade the mechanism of resistance.

Known causes of the problem from point of view of animal handling

Antimicrobial resistance is far from confined to humans and the healthcare system. We should be aware that about 50% of the tonnage of antibiotics (EFSA Journal 2009; 7(11):1372) (1200 Tons in France) is used in the treatment of diseases in animals. Fortunately in the EU, the use of antibiotics as growth promoters is banned since 2006 and has led to a lower prevalence of antimicrobial resistance in some animal bacterial populations, however, its use is still allowed

in other non-European countries. Thus usage of antibiotics in animals, particularly for treatment and the purpose of meat production (growth promoter), causes selection of resistant bacteria that can then spread to humans through food consumption, the environment, or close contact with animals. In this matter merging data demonstrate a rapid rise in bacteria resistant towards antibiotics of the beta-lactam type, especially in the poultry industry. Moreover most of the resistance present in humans has been described in animals including resistance to third generation cephalosporins (ESBL: plasmidic extended spectrum beta-lactamases) and many examples of sampling of different types of food in particular retail meats were shown to harbour species with important resistances to human (Clin Microbiol Infect 2010; 16: 33–38). Thus it is safe to conclude that, just as in human populations, the excessive use of antibiotics in animals increases the risk of developing resistance.

It is worth mentioning in this scheme the possible role of the effluent. Many publications show that at the end of the processing of effluent there is a residual resistant bacteria contamination. This has been well demonstrated for *E. coli* harbouring ESBL (Applied and Environmental Microbiology, 2010. 76: 4772–4779).

Known causes of the problem from the health management point of view

The EU has given recommendations on a strategy for the prudent use of antibiotics (COUNCIL RECOMMENDATION (2002/77/EC) ON THE PRUDENT USE OF ANTIMICROBIAL AGENTS IN HUMAN MEDICINE) to prevent sales of systemic antimicrobials without prescription. However, these recommendations are not strictly followed all over Europe. Even if they were followed, the problem of overuse would remain due to lack of diagnostic kits able to differentiate viral from bacterial infections in the hospital and mainly in the community. To avoid scaling of antibiotherapy resistance, rapid diagnostic of the infecting bacteria, and susceptibility of the invader(s) should be known as fast as possible. One of our most important goals should be reducing the time to obtain an antibiophenotype that allows the best choice of antibiotic in terms of optimum response and least impact in terms of ecology of resistance. At the present time the engineering of such a test is possible but no single technology has reached the capability and the cost of the antibiogram.

Lack of novel antibiotics are evidenced by the therapeutic deadlock in front of MDR strains. It probably will take years before the discovery of non-toxic compounds, clinical trials and lastly assessment of their use in the clinic. However, there is now no other issue more relevant than searching for novel drugs especially against Gram-negative bacteria.

Implementation of measures concerns the inter-human transmission and key recommendations to detect them, including knowledge of national and even local epidemiology, must be raised to avoid resistance dissemination. Hospital systematic searches and isolation of patients infected or colonized by specific resistant strains are common safety measures. These measures require up-to-date hospitals to follow up such recommendations. This is not the case everywhere in the EU, even not in some parts of the wealthiest countries. Other protection measures such as hand washing, or use of disposables have to be reinforced through continuous education of the medical personnel.

In this picture one should take in account that MDR strains are now slowly entering the hospital from the community and that acquisition of unusual MDR strains from abroad (carbapenemase NMD-1 for example) is becoming a real threat.

2. Consequences of the problem

Health consequences

The main consequences for health are morbidity and mortality. Different studies have been trying to asses this burden, among which we find the ECDC/EMEA technical report (The bacterial challenge: time to react; EMEA 576176/2009). It was estimated that about 400,000 infections were caused by resistant strains in Europe in 2007. Extra deaths were calculated to be more than 25,000 and extra hospital days to be more than 2.5 millions. This does not account for some indirect consequence as aftermaths severe infections due to resistant pathogens (meningitis for example) or those associated to large surgery necessary to cure the infected site. It also does not estimate deaths which may occur in the non hospitalised population.

It has been well demonstrated that in severe infections a higher risk of mortality was linked to infections due to resistant strains (Lambert et al - www.thelancet.com/infection Published online December 1, 2010 DOI:10.1016/S1473-3099(10)70258-); E.coliESBL: De Kraker et al - J Antimicrob Chemother doi:10.1093/jac/dkq412).

Societal consequences

The report by ECDC/EMA estimated the overall direct costs to society in terms of extra health-care costs and productivity losses total € 1.5 billion each year. However, the indirect costs to European countries are likely to be several-fold this amount (Conference report; Innovative Incentives for Effective Antibacterials, 2009). To avoid epidemics caused by MDR strains, costly control and prevention measures need to be taken. This cost includes not only the staff which are directly in charge of the infection control but all the dedicated personnel of the ward during an epidemic. Other costs are those of the microbiology lab which has to search for the bacteria in the infected patients but also in all the contacts 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 whole wards.

Treatment selection, in particular of the youngest and the oldest patients, may be difficult for the prescriber in absence of a precise rapid diagnostic. Physicians may have difficulties to avoid the insistence of the patient to be treated, raising the danger of selection of resistance in the global population.

While at the individual level people are concerned when it comes to their families and acquaintances, it is obvious that the population is not aware of the scale of the threat. There is a need to inform and educate the public so that it is understood why all this money has to be spent, and also to invite them to participate in the fight against resistance (hygiene, prudent use of antibiotics…). Thus, models are needed to evaluate these costs in comparison with the potential long-term health risks if nothing is done, conducting a well-designed formal decision analysis.

3. Innovation 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 developed.

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 (1 billion EUROS), and the fact that many candidates fail during the process adds to the cost. Even if the "golden antibiotic" were found, it might be limited in its indications and considered to be put for "reserve" in order to avoid it jeopardized, resulting in limited use and therefore less gains for the company. While the industry may be strong in high-throughput screening, chemical libraries, and have other large-scale advantages it has limited resources for basic science, and their organisations are incapable (or has no will) to generate the large number of basic research findings necessary to feed the pipeline.

As highlighted in the joint report from ECDC and EMA, the current pipeline of new antibiotics is running dry, especially for agents to treat infections due to MDR Gram-negative bacteria. New classes of drugs providing adequate treatment against some pathogens such as *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* are urgently needed. In particular, no drug is currently in development against MDR Gram-negative bacteria harbouring carbapenamase metallo-enzymes which are becoming the real threat.

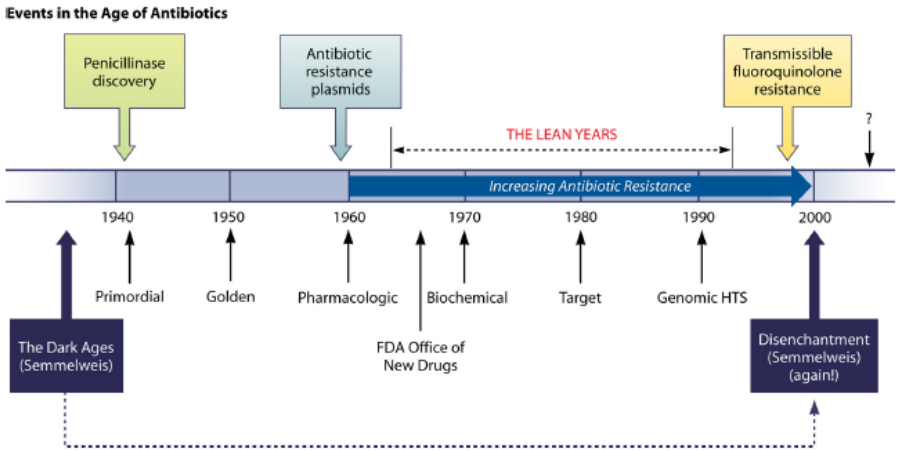


FIG. 1. History of antibiotic discovery and concomitant development of antibiotic resistance. The dark ages, the preantibiotic era; primordial, the advent of chemotherapy, via the sulfonamides; golden, the halcyon years when most of the antibiotics used today were discovered; the lean years, the low point of new antibiotic discovery and development; pharmacologic, attempts were made to understand and improve the use of antibiotics by dosing, administration, etc.; biochemical, knowledge of the biochemical actions of antibiotics and resistance mechanisms led to chemical modification studies to avoid resistance; target, mode-of-action and genetic studies led to efforts to design new compounds; genomic/HTS, genome sequencing methodology was used to predict essential targets for incorporation into high-throughput screening assays; disenchantment, with the failure of the enormous investment in genome-based methods, many companies discontinued their discovery programs. Other milestones in this history include the creation of the FDA Office of New Drugs after the thalidomide disaster led to stricter requirements for drug safety, including the use of antibiotics. This slowed the registration of novel compounds. Before antibiotics were discovered, Semmelweis advocated hand washing as a way of avoiding infection; this practice is now strongly recommended as a method to prevent transmission.

From MMBR 2010 74 417-433 Julian and Dorothy Davies.

There is an urgent need for interdisciplinary and public–private partnerships to support research in this area. Exchanges between industry, public health bodies, and academic bodies will entail not only sharing costs, but also co-ordination of the respective research activities. The solution may lie not only in scientific discovery but also in the economic incentives for developing new drugs. Public–private partnerships could provide one solution. A global pact would require that not only industry but also governments, physicians and pharmacists join forces to preserve the new medicines that our children and grandchildren need.

The genomics revolution, that was considered to have the potential to provide an abundance of targets, has not yet managed to deliver effective new antibiotics. It is likely that traditional approaches to the development of novel antibiotics have modest potential for future success and we believe it is essential to explore new paradigms for anti-infective therapy. New paradigms for drug discovery need to be defined and implemented as the major international pharmaceutical companies (“Big Pharma”) are unlikely to continue to develop new antibiotics as they have in the past.

The feasibility that a three way partnership of commercial organizations, academia and government agencies can cooperate in order to discover, develop and market both new drugs and new approaches for the treatment and control of infections should be explored. New approaches could include anti-virulence strategies, the use of agents that compromise resistance mechanisms, new modalities such as light-activated drugs and modulation of host immune processes.

4. Vision and mission of the JPI Antimicrobial Resistance

The Vision

In the next fifteen years, a significant number of Member States and Associated Countries will have built a European Research Area in the field of Antimicrobial Resistance. 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 antimicrobial resistance, reverting its increasing trend, and leading to the sustainable use of antibiotics and treatments for infectious diseases. At the end of this period, there will be scientific evidence on how to achieve a balance between resistance and effective treatments, a balance that is sustainable in time and achieved at the lowest possible level of resistance and most importantly, multidrug resistance (MDR).

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 JPI Antimicrobial Resistance (AMR) is proposed based on the assumption that AMR needs a systems and ecologic approach, because AMR will not disappear. The JPI AMR will enable Europeans to maintain the problem at an affordable level, at the lowest possible cost. The JPI aims at several interdependent goals:

- Find routes for novel antibiotics and new anti-infectious strategies.
- Scientifically validate means to increase the number of patients treated early with the appropriate antimicrobial.
- Provide scientific evidence on ways to reduce the spread of resistant strains.
- Provide scientific evidence on strategies to reduce the number of patients with resistant or MDR strains, at any level of antibiotic consumption.
- Reduce the consumption of antibiotics.

The mission

The mission of the JPI AMR is to develop scientific proposals for a sustainable use of antibiotics to treat infectious diseases in Europe, and for a decrease in the number of patients with resistant infections. To do so, AMR will achieve a European Research Area in the field of antimicrobial resistance, coordinating the best resources and capabilities for this common purpose.

JPI AMR will define a Strategic Research Agenda with three scientific areas:

- Biology and dynamics of resistance
- Prevention of resistance and innovation of treatment options
- Epidemiology and disease burden

An important element of the mission of JPI AMR will be to connect and collaborate with the different stakeholders involved in its mission. Apart from the research community, AMR will

invite the industry to discuss their needs in terms of scientific support to stimulate their interest in the field. Health care services organizations and professionals will be invited to provide their experiences and to frame the questions to be responded by this JPI. Public administrations will provide their input on policies related to pharmaceutical treatments, patient safety, transnational collaboration in surveillance, and public health.

Research resources needed

The JPI AMR will have to coordinate the best existing resources in the field of AMR, and make a sensible use of them. JPI AMR will build a European Research Area, meaning that the best available human resources are involved, that programmes are coordinated so as to achieve the needed critical mass, and that AMR takes advantage of European Research Infrastructures Consortia (ERIC).

JPI AMR will define a European policy on human resources in the field, including training programmes and the provision of the necessary job posts according to the Strategic Research Agenda. Stable and sustainable collaboration between existing research networks and research centres will be built. Funding programmes will be coordinated at European level.

Depending on the different research methodologies needed, JPI AMR will have to coordinate its work with the appropriate ERICs, or even inspire new ones. BBMRI, EATRIS, ECRIN and ERINHA at least provide infrastructures that are relevant for AMR. Observational studies may be needed, and building data bases or even cohorts may be necessary. JPI AMR will also coordinate its tasks with related European initiatives. Policies on human resources (Euraxess initiatives), research programmes of the Commission, Innovation Europe are clear candidates.

Governance structure

This coordination task will be supported by the adequate management procedures and governing structures. A Management Board will be formed, advised by a Scientific Advisory Board and a Stakeholders Advisory Board. Peer review procedures have to be approved.

Managing knowledge and innovation

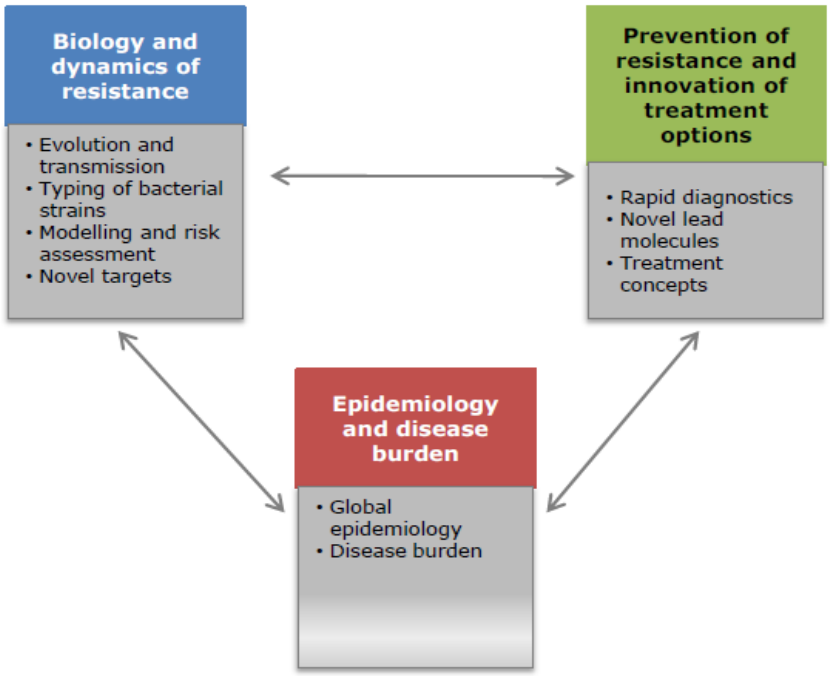
JPI AMR will have a policy for disseminating research results and for innovation. Close relations with the industrial sectors concerned, such as the pharmaceutical industry or the medical devices industry will be a crucial aspect of the mission of JPI AMR. A policy for managing intellectual property rights and criteria for an open access policy will be implemented in a coherent way, depending on the type of research results achieved.

Global networking

Given the nature of AMR, close relations with research initiatives and communities in other regions is part of the mission of AMR. Collaboration with the USA, BRICs, countries of the Mediterranean and others should be explored and promoted.

5. Research questions being addressed

The proposed work, outlined as three major blocks or themes, will be transformed into a complete set of work packages. 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.



Outline of research questions being addressed by the JPI AMR

I) 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.

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 and which factors in adhesion will allow interspecies exchanges. 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.

II) 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.

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. 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

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. The JPI will also offer opportunities to socioeconomically study the incentives required to motivate companies to engage in the development of drugs utilising such molecules. 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. Research and development on new antibacterial agents cannot be dissociated from investigations on antibacterial resistance (novel genes, genetic support of the resistance, biochemical mechanisms, structural studies of the targets, reservoirs and surveillance) and identification of novel targets.

Novel 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, phages 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.

Measures and interventions to prevent and control the emergence and spread of antibacterial resistant bacteria

Increased efforts are needed to reduce the spread of resistant strains both in the environment and in hospitals. These include:

- improving hygiene and infection control in the nosocomial and long-term facilities.
- rational use of antimicrobials
- development of new rapid diagnostic tests to distinguish between viral and bacterial infections
- new knowledge to distinguish colonization from infection in patients

Develop alternative strategies for control of bacterial infections in animals

The antimicrobial products used for treatment of bacterial infections in food and companion animals belong to the same antibiotic classes used in human medicine and include clinically-important antibiotics such as extended-spectrum cephalosporins and fluoroquinolones. This is an unwanted situation as it promotes the selection of resistant bacteria of high zoonotic potential. Ideally future veterinary antibacterial strategies should have no impact on resistance problems in human medicine. Alternative methods or products that may be tested for veterinary use include:

1) Management and intervention strategies aimed at controlling the occurrence of clinically-important resistant bacteria in animals or at preventing their transmission to humans.
2) Non-antibiotic strategies (probiotics, phages, drugs reducing the antibiotic selective effects in the gut, etc.)
3) Antibacterial compounds that are structurally and functionally unrelated to human drugs, do not select for resistance to human drugs, and have no potential use in human medicine due to their chemical or pharmacological properties.

III) 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.

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.

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.

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.

6. Added value of the JPI Antimicrobial Resistance

The expected added value of a JPI on AMR comes from three sources. The first is the creation of the coordinated critical mass needed to make a substantial contribution to address the problem of antimicrobial resistance and limit its consequences. The second is the pooling and coordination of the best quality resources in Europe for this purpose. The third is that only solutions that are valid and effective across the European Union and innovative proposals that are locally adapted have an opportunity to control the problem of AMR. Only collaboration between Member States and Associated Countries will make a significant difference.

No single country by itself is able to achieve the critical mass needed. While many of these countries 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. Hence, 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 targeting 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, such as European FP7 projects and funding opportunities exist, only a 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. Moreover, the transnational cooperation will enhance the societal impact that is required in this area, promoting knowledge dissemination among multiple sectors of the society that are implicated – patients, clinicians, pharmacists, food producers, veterinarians, and representatives of the pharmaceutical industry.

Some specific topics to be addressed (to be included in the Vision Document?)

- 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
- Identify strategies for control antibiotic resistance in animals
Even a small contribution by veterinary antibiotic use to clinical resistance problems in humans should not be tolerated. The goal is to identify at least 5 new strategies for control or eradication of clinically-relevant resistant bacteria in animals.
- The need for new antimicrobials.
- Rapid tests for infection diagnosis
- Rapid determination of antibiotic susceptibility
- Antimicrobial drug discovery, genomics and combinatorial chemistry.
- Microbial population biology and ecology of resistance.
- Antibiotic toxicity
- Structural basis of antimicrobial mechanisms
- Virulence determinants and resistance.
- Clonal spread, methods for clonal detection and characterization.
- Antibiotic consumption and infection control.
- Host-pathogen interactions in infections caused by resistant microorganisms
- Epidemiology of resistance.
- Non-antibiotic approaches, immunotherapy.
- Vaccination and resistance.
- Interventions to control resistance.
- Clinical outcome of antimicrobial-resistant infections.
- Control of antibiotic resistance in animals
- 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.