Strategic Research Agenda

Joint Programming Initiative on Antimicrobial Resistance

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Foreword

Humanity has always been under constant threat from infectious diseases. Antibiotics, therefore, are considered one of the greatest discoveries of the 20th century, because they save millions of lives from once-deadly diseases. Unfortunately, antibiotics have become victims of their own success because the misuse of antibiotics in humans and in animals has led to the emergence of resistance among clinically important pathogenic bacteria. Every dose of antibiotics creates selective evolutionary pressures, which might result in the pandemic spread of highly resistant bacterial clones. Since these clones cause pandemics that evolve slowly, they gain less media attention than other rapidly evolving pandemics caused by SARS, avian flu, or swine flu. This does not mean, however, that they are any less important. The World Economic Forum's Global Risks 2013 report concluded that, '*While viruses may capture more headlines, arguably the greatest risk of hubris to human health comes in the form of antibiotic-resistant bacteria*'.

The Global Risks report was developed from an annual survey of over a thousand global experts from industry, government, academia and civil society who were asked to review a landscape of 50 global risks. Clearly, the initiatives of several international organisations addressing the problem of antibiotic resistance, such as the World Health Organization, the European Commission, the European Centre for Disease Prevention and Control (ECDC), and ReAct (Action on Antibiotic Resistance), have been highly successful in raising global awareness among experts.

The Joint Programming Initiative (JPI) on Antimicrobial Resistance (AMR) provides an excellent opportunity to foster joint research between EU Member States that intend to address the emerging problem of antibiotic resistance. Existing research projects have usually had to compete for grants with projects from other research areas since there have been almost no research programmes specifically focusing on AMR. This approach cannot provide the sustained, long-term funding required to solve major research questions concerning AMR. In addition, research activities in this area are not harmonised between countries, which may lead to duplication of the research activities in different countries. This JPI aims to coordinate European research on AMR in close collaboration with the funding instruments of the EU, specifically Framework Programme 8 (Horizon 2020), Innovative Medicines Initiative (IMI) and the ERA-NET scheme.

The main focus of the JPI AMR is on antimicrobial resistance and human medicine. However, veterinary and environmental aspects of AMR are closely interlinked and form an integral part of the problem in human clinical medicine. We therefore advocate a holistic approach. The Scientific Advisory Board (SAB) of the JPI AMR has been established to elaborate a common scientific vision for the JPI; which is in line with global priorities. Collaboration with stakeholders, scientists and other prominent members within this field made this agenda a reality. The research issues identified as having the largest impact on society have been divided into six priority topics that together form a multifaceted approach. The topics and their research activities are a matter of urgency for Europe and reinforce Europe's

contribution to global public health, have high expected returns on investment and are complementary to each other and existing research programmes, and have clear links and synergies within and across themes.

The SRA should deliver innovative and novel approaches to make sure that we can still treat bacterial infections successfully with antibiotics in the 21st century.

Herman Goossens
Chair, Scientific Advisory Board

Mats Ulfendahl
Chair, Management Board

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Executive summary

Unlike the therapeutic advances through which acute diseases have been transformed into chronic diseases (e.g. anti-retrovirals for HIV patients), antibiotics are true miracle drugs that can completely cure patients who suffer from life-threatening illnesses. Antibiotics have saved millions of lives from once-deadly diseases. But antibiotics are misused in both humans and animals[A]. Every dose of antibiotics creates selective evolutionary pressures, which can result in bacteria becoming resistant to multiple antibiotics. These resistant bacteria can then spread pandemically over the entire planet. Infections with multi-drug resistant bacteria are a major threat to human health since correct antibiotic therapy may not be started in time or because there are very few antibiotics that can be used for the successful treatment of infections with these bacteria. The World Health Organization currently considers antibiotic resistance[B] one of the three greatest threats to human health. A return to the pre-antibiotic era would not only mean that classical bacterial epidemics would again become a major threat to public health but it would also threaten some of the most valuable therapies of modern medicine, such as transplantation programmes and immunosuppressive chemotherapy, which would be impossible to undertake without antibiotics as supportive treatments. The global and multifaceted problem of antimicrobial resistance demands comprehensive and creative solutions, which require action from many sectors of society.

The Joint Programming Initiative

Joint Programming is the process by which Member States define, develop and implement a common strategic research agenda based on an agreed vision on how major societal challenges can be addressed, that no individual Member State is capable of handling independently. The Joint Programming Initiative on AMR has 19 participating countries[C]. The JPI on AMR will develop integrated approaches to pursue unique world-class research on AMR that will be translated into new prevention and intervention strategies that improve the public health and wellbeing of populations, and delivers economic and societal benefit throughout Europe and beyond. An important element of the mission of the JPI AMR will be to connect to and collaborate with the different stakeholders involved in its mission. As well as the research community, the JPI AMR will invite industry to discuss their needs in terms of scientific support to stimulate their interest in the development of novel antimicrobials and alternatives to antibiotics. Healthcare service organisations and professionals will be invited to provide their experiences and to frame the questions to be responded to by this JPI. Public administrations will provide their input on

[A] Irresponsible usage of antibiotics includes the use of dosages that are either too high or too low, the use of the wrong type of antibiotic (including the use of antibiotic to treat infections that are not caused by bacteria), and poor-quality antibiotics.

[B] WHO refers to AMR in the broad sense, namely bacterial, viral and parasitic resistance.

[C] Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Israel, Italy, the Netherlands, Norway, Poland, Romania, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

policies related to pharmaceutical treatments, patient safety, and international collaboration in surveillance, public health and education.

The Strategic Research Agenda

This Strategic Research Agenda provides a framework of opportunities for countries involved in the JPI AMR and those who are willing to participate in joint actions. Joint actions will be implemented through co-operative activities that realign or link national investments in order to achieve increased impact and the provision of new funding.

Recommendations and priority topics

To reduce the threat of antimicrobial resistance:

– Antibiotics should be used prudently in people and animals.
– The development of new antibiotics and alternatives for antibiotics, such as vaccines, should be stimulated. In addition, novel, high-quality diagnostic tools are needed to promote the efficacious use of these new medications.
– A warning system should be created to enable better risk assessments to support effective policy measures to contain resistance in hospital, care, community and agricultural settings. To achieve this, surveillance systems on antibiotic use and on resistance (in humans, animals, food and the larger environment) should be standardised, improved and extended.
– Interventions are needed to prevent infection and transmission of resistant bacteria. A better, quantitative understanding of the transmission routes of AMR between bacterial populations and between different (animal, human, food, environment) reservoirs is needed to support the development of strategies and interventions to minimize the spread of resistance. Research on the effectiveness of intervention strategies and how they can most effectively be implemented is also required.

Political and societal awareness on the threat of AMR is crucial to stimulate the implementation of measures to fight the misuse of antibiotics and to stimulate innovation. Knowledge transfer and intensive collaborations between scientists and policy makers is important for the successful adaptation of measures that positively impact on AMR, have social support and are cost effective.
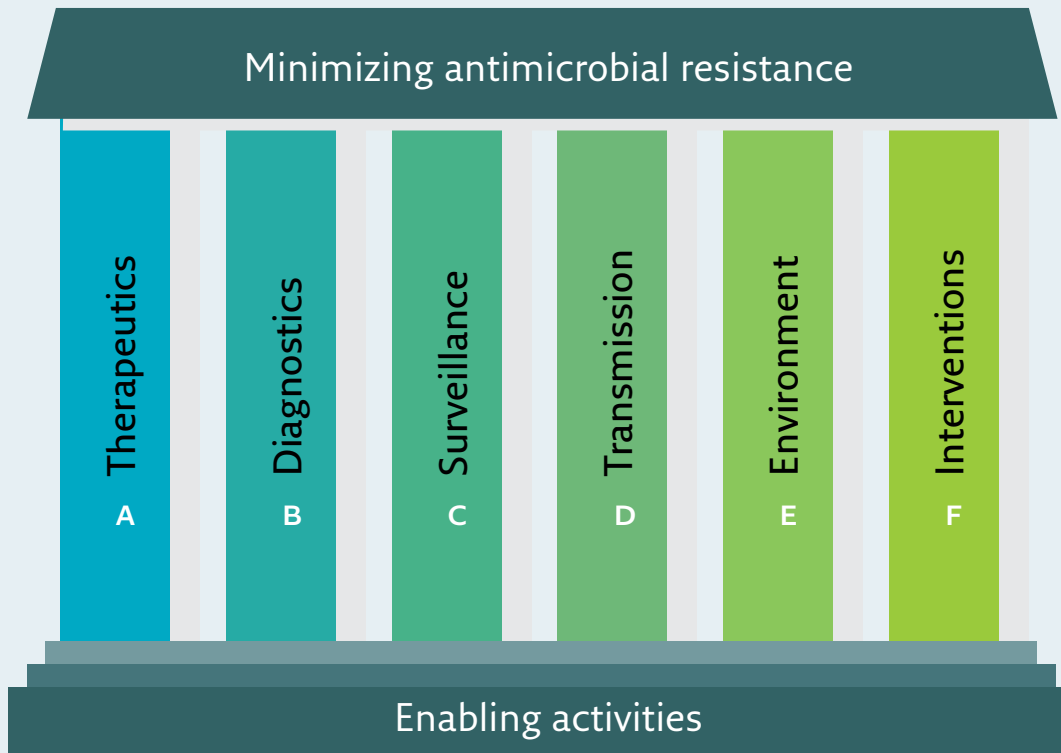
Figure 1 Schematic outline of priority topics identified in JPI AMR.

Figure 1 shows the six priority topics that cover all relevant aspects of AMR and will eventually lead to more rational use of antibiotics in veterinary and clinical settings and to a significant reduction of the risk that antibiotic-resistance poses to public health. The order of these priority areas is arbitrary but a comprehensive action against AMR should encompass all the different areas.

- *Therapeutics (A)*
  Development of novel antibiotics and alternatives for antibiotics –
  from basic research to the market.
- *Diagnostics (B)*
  Design strategies to improve treatment and prevention of infections by
  developing new diagnostics.
- *Surveillance (C)*
  Standardisation and extension of surveillance systems to establish a global
  surveillance programme on antibiotic resistance and antibiotic use.
- *Transmission (D)*
  Transmission dynamics.
- *Environment (E)*
  The role of the environment as a source for the selection for and spread
  of AMR.
- *Interventions (F)*
  Designing and testing interventions to prevent acquisition, transmission
  and infection caused by AMR.

Enabling activities and points of special interest

In order to anchor the priority topics within the larger framework of the JPI AMR, specific actions have been identified which will strengthen the impact of the different themes and research activities. These include the establishment of a biobank of clinical specimens and strains and a database containing information concerning the on-going research on AMR. This database will include veterinary and environmental samples, as these are essential for studying transmission dynamics. In addition to these activities, the JPI AMR has also identified several goals that are of special interest, specifically collaboration with stakeholders, implementation, education/training and communication. These points of special interest will form the starting point for the JPI AMR programme and individual joint actions.

Within the next fifteen years, we expect that a significant number of Member States and Associated Countries will have worked together to establish a European Research Area (ERA) in the field of AMR based on the above priority topics.

Introduction

Modern medicine often uses drugs to transform acute diseases into chronic diseases (e.g. antiretrovirals for HIV patients). In contrast, antibiotics can completely cure patients who suffer from life-threatening illnesses. In the past seventy years since their discovery, antibiotics have saved millions of lives from once-deadly infectious diseases, and continue to be crucial to the success of medical interventions. For instance, antibiotics have paved the way for interventions that were previously impossible due to the high risk of patients succumbing to post-operative infections. Also, many treatments in modern medicine, such as organ transplants or cancer treatments, would be impossible without the use of antibiotics to prevent infections that can occur due to immunosuppression.

However, antibiotics must be used prudently. Antibiotics have been misused both in people and animals because of several factors such as their low cost, easy availability (over the counter in some countries), poor understanding of their curative limits, and economic factors (in the use of antibiotics as animal growth promoters). The more antibiotics are used (even when this use is medically justified), the more likely that pathogenic bacteria will evolve resistance to antibiotics. The millions of metric tons of antibiotics that have been produced and used over the last decades have now led to a situation in which multi-drug resistant bacteria have become a major threat to human health since there are few, or sometimes no, antibiotics against such highly resistant bacteria [1]. Correct antibiotic therapy may not be started in time or there are simply no (or very few) antibiotics available that can be used for the successful treatment of infections with these bacteria. The World Health Organization (WHO) currently considers antibiotic resistance one of the three greatest threats to human health for the next decades. The global and multifaceted problem of antimicrobial resistance (AMR) demands comprehensive and creative solutions that require action from many sectors of society.

The problem

Threat of AMR

Antimicrobials are defined as all compounds that inhibit the growth of micro-organisms. Antimicrobials can be divided into groups based on the organisms that they target, e.g. antibacterials, commonly known as antibiotics, act on bacteria, while antifungals act on fungi. Although resistance to antifungals is increasing, the number of infections with drug-resistant fungi is far smaller than those caused by antibiotic-resistant bacteria. Resistance to antimicrobials among bacteria is currently perceived as a major threat to public health [1].

Antibiotics – especially broad-spectrum antibiotics – not only affect pathogenic bacteria but also the commensal bacteria our bodies contain. The human body has ten times as many microbes as human cells, and any bacterium can become resistant to one or several classes of antibiotics. AMR, which is defined as the ability of an organism to grow and survive in the presence of high levels of antimicrobials, is gained either through gene mutation or by the acquisition of genetic information from other bacteria through horizontal gene transfer. Some bacteria appear to develop resistance to antibiotics more rapidly than others.

For many years, the pharmaceutical industry has been successfully churning out new antibacterial drugs. However, it is becoming more difficult to find novel antibiotics, and many large drug companies have withdrawn from antibiotic development programmes because the process is extremely costly,

and often fruitless. Alarmingly, existing antibiotics are losing their potency due to the spread of resistance at an alarming rate while few new antibiotics are being developed.

On World Health Day, 7th April 2011, the WHO published its global strategy to slow the development of AMR by strongly advising countries to:
- Commit to a comprehensive, financed national plan with accountability and civil society engagement.
- Strengthen surveillance and laboratory capacity.
- Ensure uninterrupted access to essential medicines of assured quality.
- Regulate and promote rational use of medicines in animal husbandry and to ensure proper care of patients.
- Enhance infection prevention and control.
- Foster innovations, research and development of new tools [2].

Scope of the Strategic Research Agenda

The WHO recommendations serve as a good foundation for programmes developed within the Joint Programming Initiative on AMR and provide the focus for the Strategic Research Agenda (SRA). Many of the bacteria that can easily acquire resistance have recently emerged as important causes of hospital-acquired infections. These infections are very common (one in eighteen patients in European hospitals are affected by healthcare-associated infections [3]) and can be life-threatening, particularly when caused by multi-drug resistant bacteria. The world now seems to be entering a post-antibiotic era in which sophisticated clinical interventions (such as organ transplants, cancer chemotherapy, or care for pre-term infants) will become far more difficult due to the threat of infections with multi-drug resistant bacteria [4]. Consequently, this SRA focuses on antibiotic resistance in bacteria that can cause life-threatening infection during hospitalization. However, our recommendations are also relevant for pathogens that cause infections in community settings and which are becoming increasingly resistant to antibiotics, such as *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae*.

Prevalence, setting and trends

As early as the 1940s, Alexander Fleming, the discoverer of penicillin, warned that bacteria could develop resistance to antibiotics if the drugs were prescribed incorrectly, or inappropriate dosages were used. Now, resistance is so widespread that for some groups of bacteria, most notably in the *Enterobacteriaceae*[D], few antibiotics are effective enough for therapy. The antibiotics that still do work, frequently have major side effects, are less efficacious, or are extremely expensive. Of even greater concern are the occasional reports of resistance to these 'antibiotics of last resort' (such as carbapenems, tigecycline, linezolid, colistin, and daptomycin). Resistance to some of these antibiotics has risen quickly and rapidly as shown by the emergence of totally drug-resistant Klebsiella pneumoniae in hospitals in Southern Europe [5].

Several non-opportunistic pathogenic bacteria[E], most importantly *Mycobacterium tuberculosis* (the causative agent of tuberculosis) and *Neisseria gonorrhoeae* (the causative agent of the sexually-

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[D] The Enterobacteriaceae form a family of Gram-negative bacteria that includes several hospital-acquired pathogens such as *E. coli* and *Klebsiella*.

[E] These bacteria are not opportunistic pathogens like the bacteria that generally cause infections in hospitalized patients. Instead they can cause infectious disease in healthy populations, where the can be transmitted through human-to-human contact.

transmitted disease gonorrhea), are also becoming multi-drug resistant; thereby greatly complicating therapy of infections with these bacteria. However, the most prominent threat of antibiotic resistance in the EU is the rapidly rising tide of resistance among opportunistic pathogens[F] that cause hospital-based infections, thus worsening the prognosis of debilitated and immunocompromised individuals. Among the most important antibiotic-resistant bacteria in terms of causing infections among hospitalized patients are the so-called 'ESKAPE' pathogens. These are *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species [6]. In addition to the ESKAPE pathogens, *Escherichia coli* (*E. coli*), which is present in the intestine of all of us, remains the main cause of mortality by severe septicaemia in hospitalized patients and *Clostridium difficile*, which is an important cause of antibiotic-associated diarrhoea that can progress to life-threatening complications, are frequently resistant to antibiotics. All the above pathogens described above cause many different infections among patients including pneumonia, meningitis, soft tissue, urinary tract and bloodstream infections. Infections with these bacteria are common among hospitalized patients. For example, a one-day point prevalence study performed on May 8th 2007 showed that among 13,796 patients in 1,256 Intensive Care Units (ICUs) in seventy five countries, 51% of the ICU patients were considered to be infected. The mortality of ICU patients with infections was more than twice that of non-infected ICU patients [6].

AMR in society and healthcare settings

The direct threat of AMR to human health, in terms of mortality and morbidity, particularly in high-income countries, mainly occurs in hospitals and nursing homes among the most vulnerable patients (the young, the sick and the elderly). However, research suggests that everyone carries commensal bacteria that have acquired resistance genes [7]. For instance, even in areas where antibiotic use is non-existent or minimal, up to 50% of the population carry resistant *E. coli* [8]. Clearly, antibiotic-resistant bacteria have become so widespread all over our planet that they have become a common inhabitant of our body and can easily spread between individuals (e.g. from mothers to children, or within a family). The genes that confer resistance pose a potential threat when they are transferred to vulnerable patients or when the individual's own health declines and the healthy equilibrium with their own microbes is disturbed. Strikingly, most hospital-acquired infections are of endogenous origin, meaning that they originate from the patient's own microbiota (i.e. the microbes that live on and in the patient's body) [9]. An ageing population and the increasing prevalence of conditions like obesity and diabetes – trends seen worldwide – will cause a significant increase in the number of vulnerable members of society for whom AMR causes the biggest burden in terms of human mortality and morbidity.

In developing countries, however, the problem with AMR is even more complex because of poor water quality and sanitation and inadequate healthcare systems. The combination of a high prevalence of infectious disease in developing countries, caused by the lack of hygiene and poor access to healthcare facilities, and unregulated antibiotic use is a recipe for disaster within the context of AMR. The rising population numbers in many of these countries will further escalate the situation. Important antibiotic

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[F] Opportunistic pathogens take advantage of underlying disease or compromised immune systems of the host. These bacteria can be carried and transmitted without causing disease in healthy individuals.

resistance determinants, such as the carbapenemase NDM-1[G], which appear to have originated from resource-poor settings, are already disseminated in water and sewage systems in South Asia, and have subsequently spread all over the world. Increasing global trade and travel are factors that also favour the spread of AMR between countries and continents.

AMR, animal husbandry and veterinary medicine

AMR is tightly linked with the 'One Health' concept, which recognises that human and animal health are inextricably linked by interactions through direct physical contact with farm and companion animals, the food chain, and the environment. Therefore, the only way to regulate the threat of AMR for human health is through the cooperation and multi-disciplinary collaboration of different scientific disciplines and groups within society [10].

Antibiotics are used in large quantities in modern farming practices, either as growth promoters, as preventive measures, or therapeutically. As in humans, this use encourages the selection of resistant bacteria, which can then spread to humans though food consumption, contamination of the environment via animal manure, dust or insects that populate farms, and through direct contact of humans with animals. The extent to which the use of antibiotics in animal husbandry and veterinary medicine drives AMR in microbes that affect humans is still a subject of considerable controversy and ongoing research. Nevertheless, it is becoming more commonly accepted that in the long term, relying on antibiotics to sustain animal production is unsustainable and that measures need to be taken to minimize the misuse of antibiotics in animal husbandry. Besides being a potential threat to human health, AMR also complicates the treatment of infections in animals; which negatively impacts animal welfare and may threaten food production.

Since the EU-wide ban on antibiotics in growth promoters in 2006, European veterinarians are only allowed to use antibiotics to prevent and fight bacterial infections. However, the total amount of antibiotics used in veterinary medicine – both preventive and curative – is still too high in most EU countries. Recently, several European countries have initiated programmes to reduce, and even restrict, the use of antibiotics in veterinary medicine. Research on such programmes appears to indicate that a massive reduction in antibiotic use can be achieved with minimal cost to animal welfare and the profitability of farms [11]. The extent to which food production (of either plant or animal origin) contributes to the burden of antibiotic-resistant infections is a subject of considerable debate. However, it is important to note that much of the food that is consumed in Europe is produced in other parts of the world where antibiotic usage may be less well-regulated and therefore may be contaminated substantially by either residues of antibiotics or antibiotic-resistant bacteria.

There are key differences in the way that antibiotics are used in people and animals. For instance, livestock is commonly treated in herds rather than at the level of individuals (companion animals are an exception). In animals, antibiotics are mostly administered orally (for example by mixing through

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[G] Carbapenemases are enzymes that confer resistance to the class of carbapenem antibiotics. The carbapenemase NDM-1 (an abbreviation of New Delhi metallo-beta-lactamase-1) has only a recently emerged, but has spread widely. Resistance to carbapenems is of particular concern as these antibiotics are generally seen as antibiotic of last resort, which should only be used when other antibiotic therapies have proven to be ineffective.

feed), which exposes the large numbers of bacteria that inhabit the gut of animals to high levels of antibiotics, greatly increasing the risk of the emergence of resistance. The Food and Agriculture Organization of the United Nations (FAO), the WHO and the World Organisation for Animal Health (OIE) have collectively drawn up a list of critically important antimicrobials in both human [12] and veterinary medicine [13]. Since many antibiotics occur on both lists, a careful balance needs to be struck between using antibiotics for animal health while preserving the efficacy of particular antibiotics for human use. Therefore, veterinarians, farmers and researches alike must focus on alternatives for antibiotics such as vaccinations and other methods to prevent infections.

AMR and environment

High levels of antibiotic-resistant organisms and antibiotic resistance genes are excreted by humans and livestock in faeces, which contaminate the environment and interact with soil and animal-originated bacteria. In addition to fecal contamination, dust and insects spread organisms and resistance genes from humans and livestock to the environment [14]. This already provides a nearly limitless potential for interactions between bacteria, facilitating the acquisition of novel resistance genes. In addition, antibiotics are excreted by humans and animals during therapy, which will remain biologically active in sewage for weeks or months. This has significant eco-toxicological consequences for the microbiosphere[H].

The dose of antimicrobials present in the wider environment through animal manure and human faeces (in the form of sewage) is at levels that are too low to kill pathogens, but enough to induce selection for resistance in bacteria. Low concentrations of antibiotics can increase the mutation rate of bacteria by inducing systems that cause DNA damage and by increasing the rate at which bacteria can acquire novel DNA through horizontal gene transfer[I] [10]. Thus, low concentrations of antibiotics may lead to the emergence of novel resistance mechanisms, or the transfer of resistance genes from environmental reservoirs to opportunistic pathogens. For example, some of the genes of the Extended Spectrum Beta-Lactamases (ESBLs)[J] appear to have first evolved in non-pathogenic soil bacteria. These genes have since been acquired by Gram-negative nosocomial pathogens in which they have become a resistance determinant of major importance. Similarly, the NDM-1 resistance gene, which has only recently emerged in Gram-negative pathogenic bacteria, may also have originated in environmental bacteria [15]. Indeed, the environment is just one of many interlinked reservoirs of resistance genes. Any or all of these reservoirs may contribute to the burden of resistance in the bacteria that infect hospitalized patients (figure 2). Finally, the possible micro-ecological damage caused by antibiotic pollution in the environment, thus altering the natural proportions of organisms, and eventually influencing critical populations involved in major biological and chemical cycles, remains practically unknown.

[H] The entire population of bacteria on earth.

[I] A process in which genetic information from one bacterium is transferred to another bacterium.

[J] Extended Spectrum Beta Lactamases (ESBLs) are enzymes that are produced by Gram-negative bacteria, making them resistant to important beta-lactam antibiotics (penicillins and cephalosporins). Carbapenems are generally used to treat infections with bacteria carrying ESBLs.
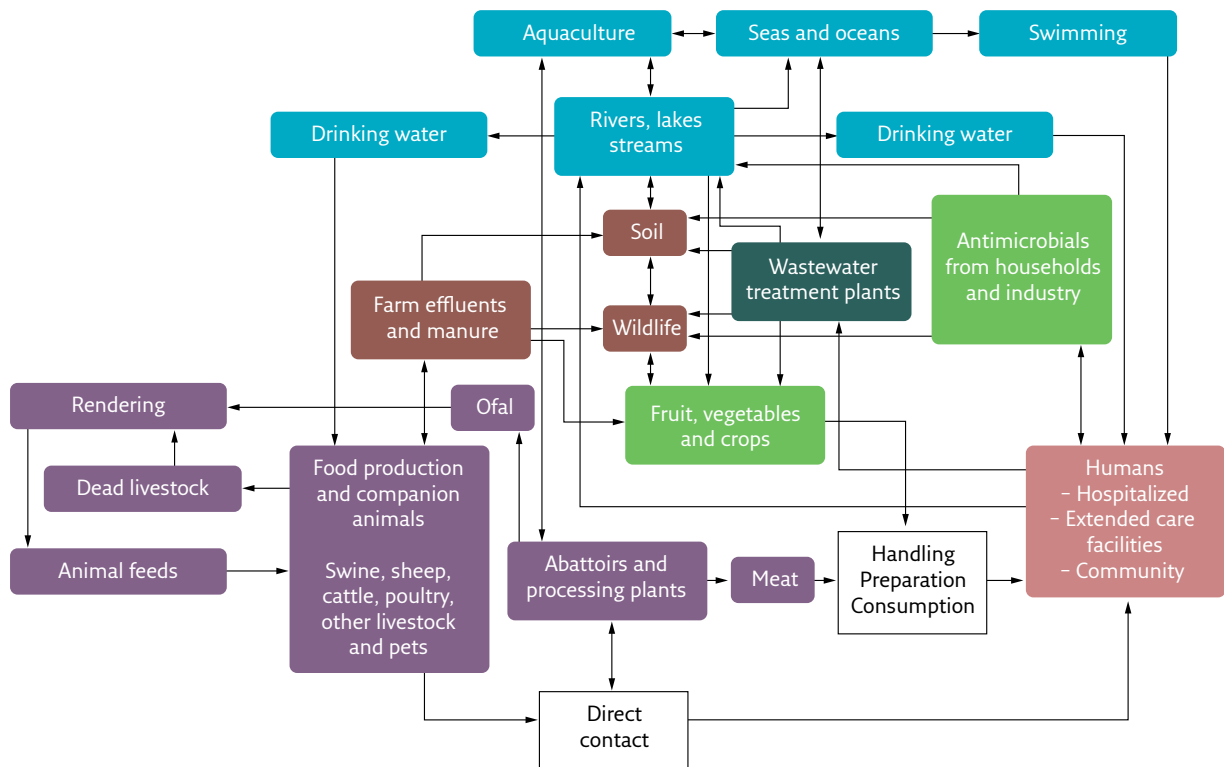
Figure 2 The complex interplay between different sectors in the spread of AMR. Adapted from Davies & Davies, 2010. Microbiol. Mol. Biol. Rev. 74:417-433, reproduced and modified with permission.

Health and economic consequences

The health risks and economic consequences caused by AMR and its future development are considered to be enormous. Different studies have tried to assess the morbidity and mortality from AMR. The ECDC/EMEA (European Centre for Disease Prevention and Control/European Medicines Agency) technical report (2009) [16] estimated that in 2007, resistant strains in Europe caused about 400,000 infections, more than 25,000 additional deaths, and 2.5 million additional days in hospital. However, these estimates are fraught with uncertainty because many countries have poor data on the burden of infections caused by multidrug resistant bacteria. In addition, a lack of standardisation in surveillance practices makes it impossible to directly compare data between countries.

Besides morbidity and mortality, AMR also has an economic impact on individuals, healthcare systems, and societies, though this cost has proven difficult to accurately quantify. To avoid outbreaks and epidemics caused by multidrug-resistant strains, costly control and prevention measures need to be taken. These costs include the labour costs of healthcare workers who are in charge of infection control measures and patient care during an outbreak, and costs incurred by microbiology labs that have to perform diagnostic cultures and contact screening during an outbreak. In the ECDC/EMEA technical report (2009), it was estimated that the overall direct costs for society in terms of extra healthcare costs and productivity losses incurred by AMR were €1.5 billion (US$2 billion) each year [17], and this

estimate did not include the costs of infection control and prevention measures. In the USA, the annual costs of AMR in hospitals are estimated at US$20 billion [18]. This is primarily caused by the considerably higher costs (estimated to be between US$6000 and US$30,000 per patient) of patients that have infections with antibiotic-resistant bacteria [19] compared to patients with infections due to antibiotic-susceptible bacteria.

The success of modern healthcare systems in extending life expectancy has come at a price. The Organization of Economic Co-operation and Development (OECD) countries have seen healthcare costs consistently outgrow the economy for decades. In most of these countries, healthcare expenditures now account for more than 10% of total GDP. According to a McKinsey report [20] by 2040, four countries (Austria, Portugal, Spain, and USA) will spend more than 20% of their GDP on health care, and only five of 21 OECD countries (Denmark, Italy, The Netherlands, Sweden, and UK) would spend less than 15%. By 2040, the USA is predicted to allocate nearly 30% of its economic output to health care. Given the impact of increased bacterial resistance on healthcare expenditure, interventions to stop the rise of AMR are urgently needed. At the same time, studies of the cost-effectiveness of these new interventions are extremely important. Therefore, more reliable and detailed information on the economic burden and costs of AMR is needed and the economic benefits of novel interventions need to be quantified.

In veterinary medicine too, the use of antibiotics is essential to treat infections in livestock. Particularly in herds of animals that are raised for food production, infectious diseases can spread rapidly, leading to major economic losses. For instance, bovine mastitis, the most common infection in dairy cows, costs the dairy industry in the USA alone up to US$2 billion annually [21]. If antibiotics can no longer be used to treat infectious diseases in livestock due to the rising tide of resistance, the economic effects would be enormous and may threaten food production systems all over the world.

Conclusion: policy recommendations

AMR is a major threat to human health in general and specifically threatens modern human medicine, as infections with these bacteria cannot be successfully treated. The occurrence of AMR is a natural phenomenon. Any bacterium can become resistant to one or several classes of antibiotics. AMR is generated either by gene mutation or by the acquisition of resistance genes from other bacteria (horizontal gene transfer). In the past couple of decades, AMR has spread pandemically while the development of new antibiotics has virtually stopped.

The unregulated and unqualified human, veterinary and other non-human use of antibiotics influences the emergence of AMR. The usage of antibiotics selects for resistant bacteria. These resistant bacteria can then spread to humans by way of food consumption, contamination of the environment and through direct contact between humans or between humans and animals. Residues of antibiotics, antibiotic resistance genes and antibiotic-resistant bacteria are excreted via effluents and sewage into the environment. From there, they can re-contaminate humans and animals, for example via drinking water, irrigation, soil or foodstuffs. A better, quantitative understanding of the extent to which animals, foods (of both plant and animal origin), and contamination of the environment can contribute to the burden of antibiotic-resistant infections in humans is urgently needed. This knowledge will be crucial

to make choices regarding interventions and policy measures in different (hospital, community, and agricultural) settings. The global and multifaceted problem of AMR demands comprehensive and creative solutions that require action from many sectors of society. Cooperation between the various national European and global agencies concerned with AMR is sorely needed, as is a coherent plan of action that includes political, socio-economic as well as scientific priorities.

Recommendations to reduce the threat of AMR:
- More prudent use of antibiotics in people and animals.
- Incentives for the development of new antibiotics, and alternatives for antibiotics such as vaccines, and better diagnostics. In addition, novel good diagnostic tools are needed to promote the efficacious use of these (new) medications.
- A warning system is needed to enable better risk assessments to support effective policy measures to contain resistance in hospital, community and agricultural settings. To achieve this, surveillance systems on antibiotic use and on resistance (in humans, animals, foods and the larger environment) should be standardised, improved and extended, with the final aim to foster a global surveillance system for AMR.
- Interventions are needed to prevent colonisation, infection and transmission of resistant bacteria by hospitalised patients. A better, quantitative understanding of the transmission routes of AMR between bacterial populations and between different (animal, human, food, environment) reservoirs is needed to support the development of strategies and interventions to minimize the spread of resistance. Research on the effectiveness of intervention strategies and how they can most effectively be implemented is also required.
- Political and societal awareness on the threat of AMR is crucial to stimulate the implementation of measures to fight the misuse of antibiotics and to stimulate innovation. Knowledge transfer and intensive collaborations between scientists and policy makers is important for the successful adaptation or adoption of measures that positively impact on AMR, have social support and are cost effective.
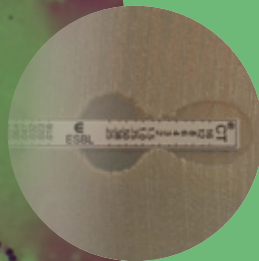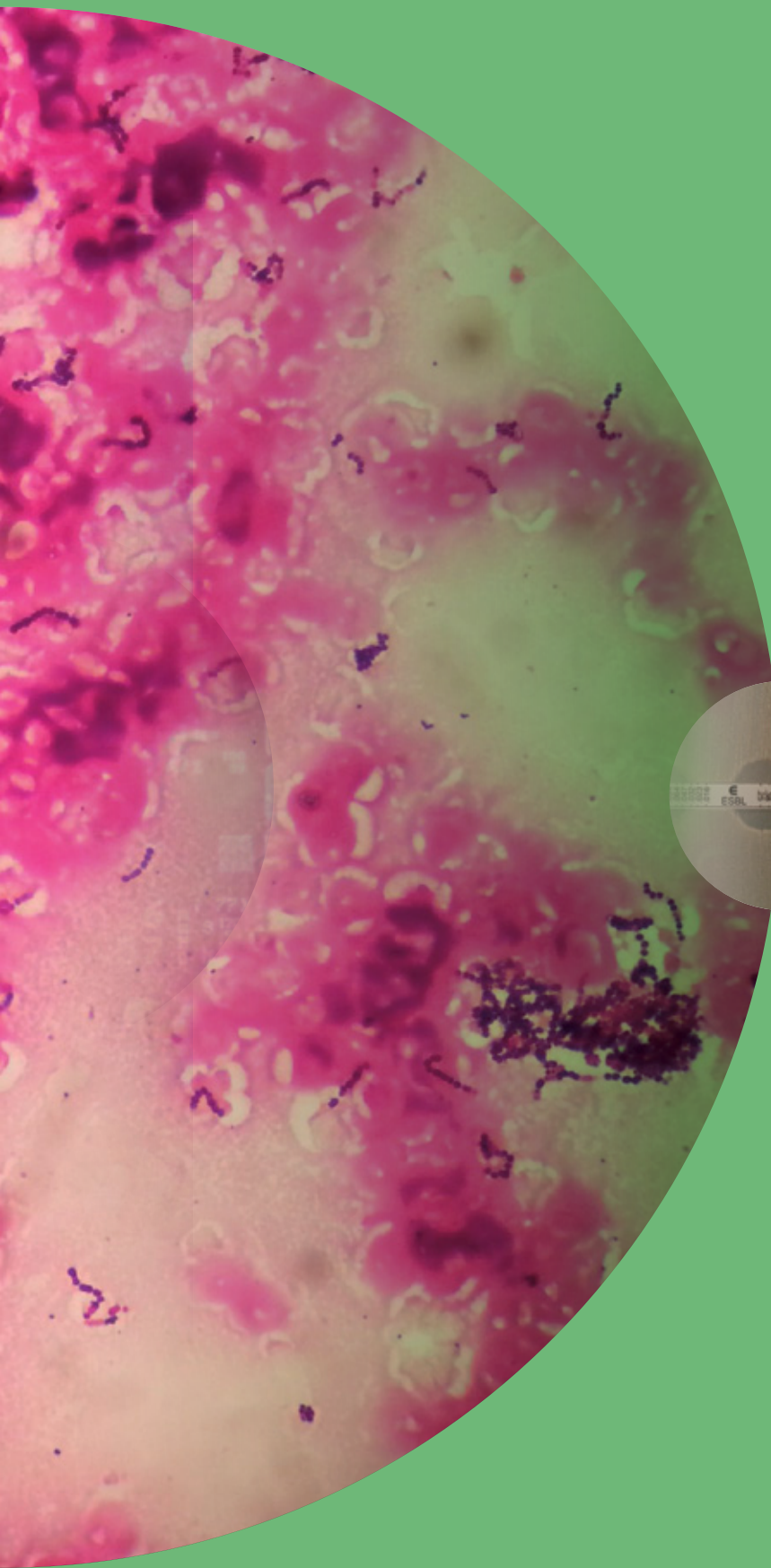
The way forward

A Joint Programming Initiative for well-coordinated and harmonised research activities

Joint Programming is the process by which Member States define, develop, and implement a common strategic research agenda based on an agreed vision on how to address major societal challenges that no individual Member State is capable of handling independently.

The Joint Programming Initiative (JPI) on AMR has nineteen participating countries[K], however only a few of these countries have a research programme focused on AMR. Most of the research projects on AMR have had to compete for funding with projects from other research areas. More alignment and coordination is needed to address inequities in resource allocation and to fund research more efficiently. Moreover, the overall knowledge regarding the global prevalence and spread of AMR and the financial and societal burden needs to be increased.

Whilst other European initiatives, such as European FP7 projects and funding opportunities exist, only a JPI encompasses the broader aspects of AMR and provides an integrated approach that is currently lacking in Europe. The proposed activities will mobilize the available national resources of several nations in an optimal way, while ensuring minimum duplication of effort and will utilize existing expert groups, and create research activities in many different fields that are relevant to AMR. This transnational cooperation will enhance the societal impact that is required in this area, promoting knowledge dissemination among multiple sectors of society involved – patients, clinical, veterinarians, pharmacists, food producers, and the pharmaceutical industry.

This SRA is the first step to draft future research programmes and will be the framework upon which the Joint Programming Initiative (JPI) will launch joint actions. Joint actions will be implemented through co-operative activities that realign or link national investments in order to achieve increased impact and to stimulate the provision of new funding.

The vision

A significant number of Member States and Associated Countries will have committed to establishing a European Research Area in the field of AMR in the next fifteen years. 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 AMR, reversing its increasing trend, and leading to the sustainable use of antibiotics and treatments for infectious diseases. This should provide crucial 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.

The global and multifaceted problem of AMR will demand vast and versatile solutions. A comprehensive solution to the problem requires action from many sectors of society. The JPI cannot address all aspects of the problem, but will show a way forward through new research and by creating networks that can sustain long-term momentum for battling the emergence and spread of AMR in all areas of society.

[K] Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Israel, Italy, The Netherlands, Norway, Poland, Romania, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

The mission

The JPI on AMR will develop integrated approaches to pursue unique world-class research on AMR that will be translated into new prevention and intervention strategies to improve the public health and wellbeing of populations, and deliver economic and societal benefit both in Europe and globally.

An important element of JPI AMR will be to connect to and collaborate with the different stakeholders involved in its mission. In addition to the research community, the JPI AMR will invite industry representatives to discuss their needs in terms of scientific support and to stimulate their interest in the development of novel antimicrobials and alternatives to antibiotics. Healthcare service organisations and professionals will be invited to share their experiences and to frame the questions to be responded to by this JPI. Public administrators will provide their input on policies related to pharmaceutical treatments, patient safety, international collaboration in surveillance, public health and education.

Implementation, impact and evaluation

The SRA is the first step to drafting future research programmes and will be the framework upon which the JPI AMR will begin joint actions. The JPI's coordination and support action (CSA) will support the development and the implementation of the JPI AMR and its SRA.

Implementation

For a meaningful implementation of the SRA, it is essential that it is adopted at the national level by the Member States and Associated States. To implement the SRA there needs to be cooperation between various national, European and global agencies concerned with research on AMR. By operating at several levels, from the scientific community to research funders, policy makers and societal stakeholders, the JPI will foster collaboration and coordination of research programmes and design a future research strategy on AMR. The SRA will serve as the framework for these efforts. Based on the SRA, an extensive trans-European work programme will be developed. First, joint actions of member states will be planned and implemented. JPI AMR will establish the foundation of real trans-disciplinary and international coordination and collaboration of European research to tackle the challenge of AMR. Furthermore, JPI AMR will contribute directly to European Commission research programmes and initiatives, e.g. to the upcoming research and innovation framework programs Horizon2020, and the Innovative Medicines Initiative (IMI). Moreover, overlaps with existing initiatives will be analysed to identify potential gaps and priorities for joint activities. In general JPI aims to stimulate cooperation between the various national European and global agencies concerned with AMR, with a coherent plan of action that includes political, socio-economic as well as scientific priorities. Thus, prioritising the different aims and research activities of the SRA will be an ongoing process within the Management Board of JPI AMR through mapping exercises on knowledge gaps and possibilities for international collaboration.

Impact

Over the next decade, the JPI AMR aims to achieve the following impact:
- Reduction of inappropriate consumption of antibiotics, both in humans and animals.
- A positive impact on treatment, care, and quality of life for patients infected with AMR organisms.
- Increased visibility, at a political level, of the burden of AMR and the benefits of research.

- A catalytic effect on the development of national and international strategies in JPI AMR countries.
- The development and implementation of new preventive and therapeutic approaches and interventions for AMR.
- Research elements relevant to AMR to be embedded more routinely in health service and care infrastructures.

Evaluation

To assess output, and short-term and long-term effects of the JPI AMR, a monitoring and evaluation framework will be created to develop a set of key performance indicators. This framework will be built in close collaboration with stakeholders and other JPIs, and will align the JPI AMR objectives (on both scientific and policy levels) with the scientific priorities, points of special interest, and enabling activities presented in this agenda. Monitoring and evaluation of the initiative will occur at different, but interrelated, levels with the approach focussing on the initiative's process and progress on its aims, such as delivery of the scientific objectives and interaction between the scientific community and wider society.

Implementation strategy

JPI AMR is based on the premise that tackling resistance requires a system-wide and an ecological approach, as AMR is an inherent part of microbial life on earth. JPI will enable Europe to contain the problem at a reasonable level, at the lowest possible cost.

Points of special interest

To achieve the aims of the JPI AMR the following points are of special interest; both at project level and at the level of the JPI AMR as a whole. These points of special interest aim to insure the social grounding of the joint actions and to stimulate the synergism between the joint actions and its projects.
- To stimulate knowledge transfer, education and training.
- To create the conditions necessary to implement research results.
- To stimulate national research agendas and align with research requirements.
- To foster collaboration with research funders globally, beyond Europe.
- To foster collaboration between research, policy, and practice and a system-wide and an ecological approach.
- To stimulate public-private partnerships (PPPs).

Excellent science alone will not necessarily contribute to a solution for the societal challenges posed by AMR. Rather, collaboration with all concerned stakeholders is essential to achieve the impact that the JPI AMR aims to attain. A key factor and indicator of the success of the JPI AMR will be direct communication and engagement with all the stakeholders including funding organisations, policy makers, scientists, physicians, patient organisations, and industry representatives, in Europe and beyond. This is because transparency of the results of research and other results of joint actions is of particularly high importance. In addition, supporting key stakeholders with appropriate information at relevant times will maximise both the support for the JPI AMR and the involvement of participating member states in the collaborative initiatives. Meaningful involvement of relevant stakeholders in research projects is an important principle of the JPI AMR, especially the involvement of patient

organisations. The perspective of stakeholders is helpful in ensuring that a project makes a correct and comprehensive problem analysis, and sets objectives and activities that will contribute to finding solutions to the core issues of AMR. Many of the research themes identified in this SRA require a multidisciplinary approach, involving scientists from non-medical or non-biological fields of science, such as social sciences, economics and industrial design and technology.

Industry is a key stakeholder. The perspective of institutions that cover the costs of health care (such as health insurance companies) at an early stage will allow novel approaches to be developed that are feasible from an industrial and economic perspective. Industry is also an important partner in diagnostics research, and in understanding how to reduce the contamination of the environment with AMR and antibiotic residues. Pharmaceutical companies are an important partner in the development of novel antimicrobials and alternatives to antibiotics. Many large pharmaceutical companies have withdrawn from antibiotic development programmes mainly because of the perception that antibiotic development is associated with low (or even negative) revenues. Push and pull measures by governments and their public organisations are needed to stimulate the involvement of industry regarding the development of new antibiotics and alternatives for antibiotics. As a consequence of pharmaceutical companies downsizing their antibacterial drug discovery programmes, there is a gap in early stage research and development that jeopardises the discovery of novel leads.

This gap cannot be bridged by academic partners only, as they lack the necessary expertise in pharmaceutical development. Small- and medium-sized enterprises (SMEs) are well positioned to do the job but access to funding and partnering is challenging for those companies. In the joint actions of JPI AMR, SMEs that focus on antibiotic discovery and development should be embedded in collaborative networks. Public-private partnerships will be vital in driving research into AMR as it combines the knowledge and capacity of academia and industry. However, in a PPP, the open exchange of knowledge is crucial, and thus the development of a meticulous strategy on intellectual property rights by JPI AMR is an important task.

Enabling activities

In order to anchor the priority topics within the larger framework of the JPI AMR, specific requirements have been identified which will strengthen the impact of the different themes and research activities.

Developing a publicly accessible database of research activities in the EU

JPI AMR is engaging in a mapping exercise to understand the different nationally and EU-funded research programmes and projects related to AMR. This mapping should ensure that research is complementary and that there are no major overlaps, aid in identifying gaps and research opportunities, assist in decision making for the different funding bodies, and enable the monitoring of the impact of research. While attention will naturally be focused on addressing research at national and European levels, AMR is a global issue. Because of the major public health implications and societal relevance of research into antibiotic resistance, scientific articles should be published under an open access license to make them broadly available to scientists, policymakers, and the general public.

Developing a biobank of clinical specimens and strains

The JPI AMR will promote open-access to encourage the sharing of data and materials. A biobank containing high-quality materials (including reference strains that carry known and newly identified antibiotic-resistance genes) should be created by promoting best practise in sample collection, curation, and handling. This database will include veterinary and environmental samples, especially because these samples are important for the study of transmission dynamics. Standardised methods and tools for data collection, storage and analysis should be developed and promoted in collaboration with researchers and stakeholder organisations. Possible collaborations and synergy with existing research infrastructure initiatives will be explored.

The following aspects should be taken into account when developing the database and biobank outlined above:
- An inventory of existing databases and biobanks, and the creation of new biobanks.
- Encourage integration and harmonisation of data and materials, and to promote an open-access approach to sharing data and materials.
- Standard operational procedures, that include ethical and intellectual property issues, should be developed for access to the databases and biobanks in addition to software and technologies to improve the collection and sharing of information.
- Link existing cohorts, patient registers, and collections of samples and data through previously funded research projects on AMR. This will require the development and implementation of new software and technologies to improve data mining and sharing of information.

Six research priorities: the aims, activities and synergy

To achieve the overall aim of the JPI AMR – a reduction of the burden of AMR by 2040 – six research priorities have been identified that take into account the scientific, clinical, and societal importance of this subject. These research activities highlight different aspects of the challenges that are currently being posed by AMR. Together, these priorities form a comprehensive approach for studies into strategies that will reduce the use of antibiotics, and which will minimise the emergence and spread of antibiotic-resistance genes and antibiotic-resistant bacteria.

The priority topics which have been identified cover a wide range of approaches that should ultimately lead to a reduction of the threat of antibiotic resistance in clinical practice. Because of the complex nature of AMR (figure 2, page 20) a comprehensive approach is needed to fully cover all relevant aspects that contribute to the emergence and spread of AMR. Consequently, research activities that are suggested in this SRA are diverse and cover a large number of domains (bacteria, patients, health care systems, veterinary reservoirs of AMR and global ecosystems). Some activities will have no effect for a decade or two, but we will regret not having started them since they will eventually be important. Others are more directly necessary for finding solutions in the near future. Table 1 offers an overview of the focus of the six priority topics and their main research activities and aims. The priority topics will be further elucidated in the following chapters.

Priority topic	Focus	Research objectives/activities
A - Therapeutics	The improvement of current antibiotics and treatment regimens, the development of new antibiotics and therapeutic alternatives to antibiotics.	– To find new targets for antibiotics. – To develop new antibiotics. – To improve pharmacokinetics and pharmacodynamics of neglected antibiotics. – To develop treatment protocols based on combination therapy using existing and new antibiotics. – To develop alternatives for antibiotics (e.g. vaccines). – To develop and study effect of policy measures and economic stimuli to minimize barriers for the development and introduction of new antibiotics.
B - Diagnostics	The improvement of diagnostics and the development of novel (rapid) diagnostics to stimulate better use of current antibiotics and support the development and use of new antibiotics and alternatives to antibiotics	– To improve existing and develop new diagnostic tools that more effectively distinguish between viral and bacterial infections. – To improve existing and develop new diagnostic tools that can promote the use of narrow-spectrum antibiotics. – To improve existing and develop new diagnostic tools for the identification of antibiotic resistant bacteria; including their resistance profile. – To identify and remove current barriers that inhibit the acceptance of rapid diagnostic tests.
C - Surveillance	The establishment of an international, standardized surveillance programme for AMR and antibiotic use in human, and agricultural settings	– To perform operational research on the standardisation and extension of existing surveillance systems. – To perform a pilot study on the feasibility of a global phenotypic and genotypic surveillance programme for AMR. – To initiate a surveillance programme for antibiotic use in people and animals.
D - Transmission	A comprehensive, multi-disciplinary understanding of the transmission mechanisms by which antibiotic resistance can spread between bacterial populations and between different (animal and human) reservoir and to translate this knowledge into the development of evidence-based strategies to minimize the spread of resistance.	– To determine by which mechanisms and how efficiently AMR can spread among bacteria that populate the human and animal intestinal tract. – To determine whether food is an important vector for the spread of AMR. – To determine the effect of migration, tourism, different healthcare systems and agricultural practices in Europe on the spread of AMR. – To perform a risk assessment that will identify the important factors that contribute to the exposure of humans to antibiotics and AMR. – To provide testable hypotheses for intervention studies that are aimed at controlling the emergence and spread of AMR.
E - Environment	The assessment of the contribution of pollution of the environment with antibiotics, antibiotic residues and resistant bacteria on the spread of AMR and the development of strategies to minimize environmental contamination by antibiotics and resistant bacteria.	– To perform risk assessment studies to estimate which of the various transmission pathways from the environment to humans are the most important to address to minimize the spread of AMR. – To perform a meta-analysis of current national and international activities that are aimed at reducing the contamination of the environment by human and animal waste and by human activity with antibiotics and resistant bacteria. – To determine the exact role of various environmental reservoirs (e.g. surface water, soil, air) on the emergence and dissemination of AMR – To understand the basic biological process that underlies these phenomena to develop remediative and preventative measures.
F - Interventions	The study of preventive and control interventions that focus on improved antibiotic stewardship, compliance and prevention of transmission of AMR and to determine and improve their efficacy.	– To initiate large-scale, international projects in which interventions that are aimed to prevent and control the spread of AMR can be tested in different (health care, community, agricultural) settings. – To compare and combine AMR prevention and control practices in cost efficacy trials – To perform research to optimise implementation strategies of interventions aimed at reducing AMR.

Table 1 An overview of the priority topics and main research objectives per topic.
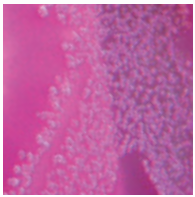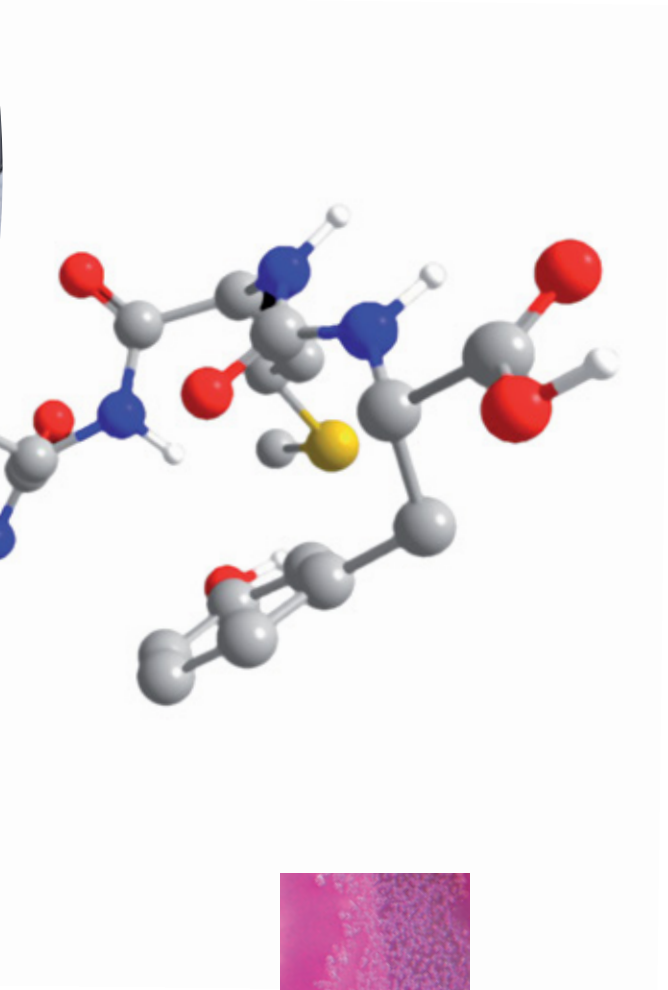
Priority topics

PRIORITY TOPIC
A

Therapeutics
Development of novel antibiotics and alternatives for antibiotics – from basic research to the market

The overarching goal of this priority topic is to stimulate basic and translational research that will lead to the identification of drug targets and candidate agents for novel antibiotics and anti-infective strategies. In addition, this priority topic will promote research that exploits old and neglected antimicrobial compounds and innovative combinations of agents as well as research into the optimization of drug use, dosage, and delivery. An additional aim is to initiate research into the possibilities and effects of minimising the regulatory and economic barriers to the introduction of novel antibiotics and anti-infective compounds.

Introduction to problem definition

In the golden age of antibiotic discovery (1940–1980), novel classes of antibiotics were discovered through screening programmes that identified antimicrobial agents that were produced by bacteria and fungi. While the success of existing antibiotics is slowly being eroded by the rising tide of resistance, the antibiotic development pipeline has dwindled to a trickle in the last forty years. Two new classes of antibiotics have recently entered the clinic in the form of linezolid, and daptomycin, but neither is active against Gram-negative bacteria. One additional new class of antibiotics, the glycylcyclines, which were derived from the tetracyclines, is active against Gram-negatives. However, resistance against all of these novel antibiotics has already been reported. The problems due to the rising tide of antibiotic resistance are not limited to Gram-negative bacteria as infections due to multi-drug resistant Gram-positive bacteria have also become a significant cause of morbidity and mortality in both hospital and community settings.

Unfortunately, many large pharmaceutical companies have withdrawn from antibiotic development programmes, mainly because of the huge economic costs of developing agents that rapidly succumb to resistance. In 2004, only 1.6% of the drugs in development by the world's fifteen largest drug companies were antibiotics. Compared with drugs used for treating lifelong chronic diseases, such as hypertension, antibiotics are used for acute conditions, meaning that they are far less profitable for the drug industry. Furthermore, antibiotics are often undervalued and underpriced compared with other therapeutic classes (e.g. anticancer agents) despite the huge public healthcare gains that have been and can be achieved by the judicious use of antibiotics [22].

Aside from these monetary challenges, the successful clinical development of novel antibacterials requires overturning strongly held views that (a) only established antibacterial targets are viable and (b) new antibacterials must be broad-spectrum. Difficulties in antibacterial drug development have been further compounded by mergers of pharmaceutical companies with have led to a loss of investment and expertise in antibacterial discovery and development. In contrast to most other pharmaceuticals, these drugs must work effectively against different bacterial species; access intracellular targets by crossing cell envelope permeability barriers, and evade efflux pumps while retaining activity in many different body compartments. In addition, numerous regulatory hurdles act as deterrents to bringing new antibacterial agents to the market and licensing difficulties and poor returns on investment are highly likely to further starve the discovery pipeline. Finally, if new antibiotics are developed, they may be designated as agents of last resort and their use could be restricted by government health agencies.

In 2008, the European Commission launched the Innovative Medicines Initiative (IMI) to foster PPPs with the aim of accelerating the drug-development process by supporting the more efficient discovery and development of better and safer medicines for patients. AMR is one of the areas in which IMI is supporting public-private collaborations. To this end, the first AMR projects were launched in February 2013 and involve: (a) the creation of a pan-European network to efficiently conduct, high-quality multinational clinical trials at all stages of the development of new antimicrobials development and (b) the discovery of novel methods for getting antibiotics into multi-drug resistant Gram-negative bacteria and preventing these bacteria from exporting antibiotics out of the cell through efflux mechanisms before they can take effect.

Given the importance of new antibiotics for human medicine it is likely that when novel antibiotics are developed they will be safeguarded for human use only and will not be released for use in agriculture or aquaculture. It is therefore essential that current treatment regimens in agricultural settings are improved and that alternatives to antibiotics, which can be used to prevent and combat infections in animals, are developed.

Opportunities

It is now widely accepted that, in the battle against antibiotic resistance, innovative scientific strategies that are likely to lead to the discovery and development of new antibacterial agents and preventative strategies need to be stimulated. IMI is crucially important in moving candidate antimicrobials that are currently in the development pipeline of pharmaceutical companies to clinical

trials and, eventually, introduction in clinical practice. IMI is not specifically aimed at fostering pre-clinical research in understanding how bacteria resist the actions of antibiotics or whether additional targets for antimicrobial therapy can be identified and exploited. However, this knowledge is fundamental for ensuring that the drug pipeline is continually replenished with candidate lead compounds with clinical potential, as new and existing antibiotics will become obsolete due to the selection for resistance.

Research into novel antibacterial therapeutics should not solely focus on the development of novel drugs that aim to kill or reduce the growth of bacteria should. Indeed, studies of alternative strategies, such as those that target virulence mechanisms, including the inhibition of adherence to host cells or the dispersal of biofilm structures, or those that are aimed at enhancing the clearing capacity of the host should also be pursued. This specifically includes the development of vaccines against multi-drug resistant bacteria. Vaccines have historically been very successful preventive measures against infection. By targeting antibiotic-resistant clones, the spread of these clones in both community and hospital settings may be minimised or even prevented. Vaccines are also widely used in veterinary medicine, where they comprise approximately 23% of the global market for animal health products [23], but the use of vaccines specifically targeted against multi-drug resistant bacteria that colonize and infect animals needs to be explored further. Research into innovative combinations of compounds (multiple antibiotics or antibiotics combined with other anti-infectives) also holds great promise, as do the development of compounds that may inhibit the emergence and transfer of antibiotic resistance. Finally, we need to create opportunities to translate fundamental discoveries in bacteriology into antibacterial drug discovery programmes and engage with industry to overcome barriers to engagement with academia. We need to strive for international harmonisation of regulatory processes with respect to the global development of new antibacterials: one could envision the establishment and maintenance of a task force with diverse academic and industrial expertise that can engage the pharmaceutical industry and drug regulatory bodies to review and comment on new anti-infective initiatives.

The introduction of novel antibiotics will be stimulated by advancements in diagnostics (priority Diagnostics, page 42), which will rapidly identify causative agents of infections and which is envisaged to lead to the development and use of targeted, narrow-spectrum antibiotics. In addition, the research in topic Interventions (page 62) will complement the research described in this priority topic as high-quality clinical trials are needed to test the efficacy of novel antibiotics.

Research objectives and activities

New antibiotics and alternatives to antibiotics

The most important activity in this priority area is to promote basic and translational research to provide leads, targets, and candidate compounds that can be exploited to develop novel antibiotics and anti-infective strategies (including immunotherapy, vaccines and anti-virulence or anti-colonisation approaches and combinations of different therapeutics). In addition, research aimed at re-sensitising resistant bacteria to conventional antibiotics should be stimulated, for example by developing novel enzyme or efflux pump inhibitors. Research is also needed to better understand why some existing

antibacterial compounds select more for resistance than others as this may guide the development of a novel generation of antimicrobials of which the use may be associated with minimal emergence of resistance. In addition, mechanistic studies into the molecular mechanisms that lead to AMR may lead to the development of compounds that minimise the emergence and transfer of antibiotic resistance. Finally, approaches that harness the ability of the human microbiota to prevent pathogens to colonise, ranging from the use of a new generation of probiotic products to faecal microbiota transplantations, may be investigated as novel prophylactic and therapeutic interventions directed towards the prevention of colonization and infection by multi-drug resistant bacteria.

Improve existing antibiotics

Although the above activities are crucial for ensuring that future bacterial infections can continue to be treated and prevented, it could take at least a decade before basic biological data will be translated into clinical products. As there is an urgent need for the rapid introduction of novel antimicrobials, the exploitation of previously discovered, but neglected, drug compounds should be promoted as they may be introduced more rapidly into clinical practice than newly developed pharmaceuticals. Several antibiotics that have been developed in the past are not, or are rarely, used in clinical practice because of poor pharmacokinetics, pharmacodynamics, or side effects. Research could now resuscitate these old antibiotics, with the aim to improve the clinical efficacy and reduce side effects, and to develop them into safe and effective antimicrobial drugs for modern clinical practice.

Research is also needed to optimise drug use, dosage, and delivery to improve the antibacterial efficacy of existing antibiotics and to reduce their adverse impact on the normal microbiota. In particular, the application of nanomedicine in the delivery of antibiotics (e.g. by coating or encapsulation of antibiotics onto or into nanoparticles or liposomes) holds great promise. In addition, the pharmacokinetic/ pharmacodynamic (PKPD) properties of neglected antibiotics need to be studied to improve the optimisation of dosing during therapy, thereby minimising toxicity, and to prevent the development of resistance. This is not only relevant for the use of antibiotics in humans, but also in veterinary settings where most antibiotics are given orally and therefore have a major impact on the gut microbiota of the animals. Research into population pharmacokinetics in animal herds or flocks, may be used to optimise antibiotic-dosing strategies, as current regimens may lead to considerable overuse of antibiotics in agriculture, which will fuel antibiotic resistance. While research into the optimisation of drug use, dosing, and delivery may mainly provide benefits in the or mid-term or long-term, in the short-term it is essential that studies are undertaken to improve methods of *in vitro* susceptibility testing and better predict *in vivo* efficacy. These novel *in vitro* susceptibility-testing approaches can then be used in subsequent PKPD-studies to optimise dosage and length of treatment for antibiotics, thereby minimising the emergence of resistance.

Regulatory and economic aspects

For each of the research activities described above, it is essential that regulatory processes are streamlined and economic barriers are lifted to allow the rapid and successful introduction of novel antibiotics and antimicrobials to the market. Ongoing activities in these fields, including cooperation between the European Medicines Agency and the US Food and Drug Administration (FDA), to improve and harmonise the processes that are needed to obtain approval for the clinical use of novel antibiotics and anti-infectives targeted at multi-drug resistant bacteria, should be further stimulated. In addition, efforts towards collaboration between academia, SMEs that work on the discovery of novel antibiotics,

large pharmaceutical companies and other private and public bodies (such as those now being set up within the IMI initiative) need to be facilitated, to stimulate the commitment of pharmaceutical companies to the development of antibacterials and in particular to ensure that promising candidate compounds are taken through the early phases into phase III clinical trials.

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PRIORITY TOPIC

B

Diagnostics

Design strategies to improve treatment and prevention of infections by developing new diagnostics

The overarching goal of this priority topic is to stimulate the design, development, evaluation and implementation of new diagnostic tests for the treatment and prevention of infections; particularly those caused by antibiotic-resistant organisms. Novel diagnostics will support rational clinical decision algorithms leading to a targeted, more sustainable use of antibiotics and tracking of AMR.

Introduction to problem definition

A radical change in the manner in which antibiotics are prescribed is necessary; up to an estimated 70% of antibiotics are prescribed incorrectly [24], i.e. when a bacterial infection may not be present. This is largely because physicians cannot make a precise diagnosis in real-time. For example, antibiotics should be used in only a fraction of patients with acute respiratory infections because most of these infections are caused by viruses, which are not affected by antibiotics. Biofilm infections are another example of hard-to-diagnose infections that are resistant to antimicrobial treatment. Unless diagnostics are improved, physicians and veterinarians will continue to prescribe antibiotics in any case in which they suspect that the patient may have a bacterial infection. Because the overall volume of antibacterial use is correlated with resistance, rapid and cheap diagnostic strategies that help in identifying those patients or animals who really need antibiotics would curtail antibacterial resistance.

The effect of the wide-scale introduction of rapid diagnostics on minimising the emergence and spread of AMR needs to be quantified. The successful implementation of rapid diagnostics also requires major behavioral changes by clinicians who will need to wait for the result of a rapid test. In addition, the success of novel diagnostics may also depend on changes in the reimbursement structures for health-care costs that are used by governments or health insurance companies.

Improved diagnostics will also advance antibacterial development, particularly of narrow-spectrum antibiotics in the following ways:

- The cost of clinical trials will be reduced by enabling focused enrollment of only those subjects infected with the targeted pathogens.
- Rapid companion diagnostics are a prerequisite to the development for some of these narrow spectrum antibiotics.

It is expected that more possibilities for rapid and early diagnostics can reduce the purely preventive use of antibiotics in veterinary medicine. Technologically, the tests for veterinary applications may not differ much from those used in human medicine. But different sampling techniques and protocols are necessary to efficiently assess herds and stables. Diagnostic tests also have to be validated for different species. It is important to involve the industry on this point.
Rapid testing may also be used in the food chain between primary production and the consumer in order to rapidly identify contamination of food products with antibiotic-resistant bacteria thereby increasing food safety.

Currently there is no roadmap for the successful development of emergent diagnostic technologies. Consequently, there is an urgent need for a plan that matches short-term and long-term goals with specific technological solutions. Academia and industry are currently both developing new detection technologies with the support of large amounts of private and public money, not always with clear guidance on urgent clinical needs. Nevertheless, novel technologies have already been developed to identify microbial pathogens and antibiotic resistance traits, and to differentiate bacterial from viral pathogens. If put to effective use, most of these technologies can decrease the time required for detection of biomolecules like proteins and nucleic acids. However, most of these novel technology platforms lack the ability to identify proteins, nucleic acids and other biomarkers simultaneously. Other issues that impede current diagnostic platforms are time-consuming testing procedures, lack of a sample preparation step, insufficient sensitivity and specificity, and high cost. Finally, many of the new diagnostic technologies have not been developed with the current reality of health care in mind, including current clinical practices, primary care and hospital infrastructure, animal managing practices, and the financial incentives of current healthcare systems. Thus, most of these novel technologies have not yet found applications in diagnostics nor have they been rigorously evaluated.

Even if these new technologies improve clinical outcomes, they typically increase costs because innovators often focus more on the outcomes achieved (i.e. a rapid outcome of the test) than on the value delivered. Therefore, we can expect that these technological innovations, which allow truly personalised human and veterinary medicine that is delivered to individual patients or animals, will raise, rather than lower costs. Consequently, if these new technologies are to be successfully implemented in the future, we will need to develop new and smarter holistic care for both human and animal populations. It must also be demonstrated that they are cost-effective and can contribute to the control of healthcare costs.

The next challenge will be to make sure that the entrenched habits of over-prescribing antibiotics are eliminated by the use of appropriate diagnostics. Articles in scientific journals, workshops and courses, or guidelines and appraisals of health technologies, will not suffice to encourage compliance with best practice and to implement novel, rational, clinical algorithms for the adequate prescribing behavior of

antibiotics. Finally, the successful introduction of early diagnostics also depends, at least in part, on the empowerment of patients through quality information and strategies to improve health literacy as health-literate patients have better health outcomes and higher quality of life, have better awareness and knowledge about medicines use, and take greater responsibility for their own health. These patients are better at providing vital information, asking pertinent questions, making more rational use of diagnostics and therapies, and using the health professional's time effectively, all of which can help reduce waste of resources. In the agricultural sectors, education efforts should be aimed at farmers who need to understand the benefits of rapid testing in terms of sustainable use of antibiotics and a reduction in economic losses from disease among their animals.

Opportunities

The development of rapid diagnostics requires secure funding for a long enough period of time to ensure development from concept to production. This could be done by encouraging PPPs to support sustainable innovation and synergy between academic centres and are driven by the needs of the users. One of the most challenging aspects of creating these partnerships is driving technology developers to focus on the real benefits for specific purchasers and to bring together disparate technologies into integrated simple systems at a reasonable cost. Another challenge is to find real markets, where a point-of-care solution really matters enough to some purchasers to drive demand and to encourage insurance companies or governments to pay for it.

The JPI AMR provides an opportunity to build a European platform to evaluate rapid diagnostic tests by aligning payers and providers, as well as involving those who use and benefit from these rapid tests. Unique collections of clinical material and strains have been gathered during the course of many EU-funded projects. These collections should be made available for the development of these rapid tests. The selection of appropriate targets for detection and identification of pathogens and their resistance characteristics is critical.

This research priority could provide the diagnostic tools that are needed for intervention trials, such as those proposed in the last priority topic Designing and testing interventions to prevent acquisition, transmission and infection caused by AMR. Such trials may also demonstrate the added clinical and health-economic benefits of these rapid diagnostics. The research of this priority topic can be strengthened by the results of activities from the other priority topics. For example, epidemiological data gathered in priority topic Surveillance (page 47) and in the topic Environment (page 57) will help to designate appropriate targets for detection and identification of pathogens and their resistance characteristics.

Research objectives and activities

Roadmap for the development of rapid diagnostics

The development of novel diagnostics needs to be driven by an existing need of stakeholders in health care and veterinary settings and other sectors where AMR is a challenge, for example, in the food industry. In addition, those who pay for diagnostics, especially healthcare insurance companies, need to be involved. Specific public health, patient and agricultural issues need to be identified where a

point-of-care or farm-solution matters enough to purchasers to drive demand and ensure that insurance companies or governments to pay a fair price. Involvement of relevant stakeholders including the industry and potential payers (specifically health insurance companies) at an early stage will stimulate that novel approaches are feasible from an industrial and economic perspective and outcomes are more rapidly translated into practical use.

Special challenges for new, and the improvement of existing, diagnostic tools are:
- The identification of patients most at risk of developing an infectious disease, as this will facilitate proactive planning and management of their care and prevent the escalation to higher cost settings.
- The development of personalised medicine in infectious diseases, to identify patients who genuinely need antibiotic therapy.
- The development of rapid diagnostic tools that support the use of narrow-spectrum antibiotics.
- The development or improvement of diagnostic tools that are capable of identifying AMR.
- In veterinary settings, novel diagnostics will also aid in rapidly identifying the causative agents of infectious diseases, which may significantly help in reducing inappropriate antibiotic use since antibiotic therapy is generally given to entire herds or stables thought to be at risk of infectious disease.

Sustainable business models

The development of novel diagnostics needs to be supported by sustainable business models that result in innovation, long-term investment, and public-private partnerships. Interactions between public and private partners will also provide a framework to plan and coordinate technology development that correspond to current and future needs of clinicians, veterinarians and food safety experts. For the next generation of novel diagnostics, new platforms that integrate different technologies need to be developed. These novel platforms should be faster and cheaper than current technologies and should enable simultaneous identification of proteins and nucleic acids (not only DNA but also RNA, by which gene expression can be determined), with a better sensitivity and specificity. For the development and validation of novel diagnostic platforms, it is essential to use standardised materials for testing. To this aim, a diagnostic knowledge base, consisting of a biobank and database, for the industry and academia will need to be established. This knowledge base will help to deliver new diagnostic tests and improve current assays. The knowledge base should include collections of several thousands of microbial strains and purified genomic DNAs, sequences of genes, panels for quality control testing and well-characterized clinical samples with relevant clinical information; which can be used to optimize and standardise novel diagnostic tests.

Clinical validity, clinical utility and cost-effectiveness

Once new diagnostics have been developed and validated, their clinical validity (in terms of improved patient outcomes that can be achieved by the introduction of the diagnostic test), clinical utility (by improving decision-making by physicians and veterinarians) and cost-effectiveness needs to be studied in different clinical settings and healthcare systems as well as farms. Well-designed pre-clinical studies and clinical trials need to be conducted to evaluate rapid diagnostic tests as well as the optimal integration and implementation of these tests. Adaptable research projects that respond to the outcomes of the evaluation studies will also be needed. In addition, the optimal integration and implementation of these tests into healthcare practice and animal production systems needs to be

evaluated. The benefits and costs of novel diagnostics will be studied by performing cost-effectiveness analyses through comparisons with standard approaches for the diagnosis of infectious diseases. The outcomes of such studies will support the appropriate use of new diagnostics and the implementation of reimbursement systems.

Identifying barriers for acceptance of rapid diagnostic tests

Barriers to the acceptance of rapid diagnostic tests can be identified through a combination of behavioral sciences, economics, and social marketing. Identification of such barriers can be beneficial in understanding behavioral factors that may help in overcoming the hurdles that may limit the use of these tests in the treatment of people and animals. Comparative studies between countries in the relative use of current rapid diagnostics in community, health care and veterinarian settings will allow the identification of factors (including differences in reimbursement and incentive systems) that hinder suitable use of rapid diagnostics in rational clinical decision-making. Mechanisms for empowering populations and farmers to create value-conscious consumers and patients regarding the benefits of rapid diagnostic tests in terms of better treatment and minimising antibiotic usage need to be identified. Based on the knowledge gathered by research in this priority topic, hypotheses for measures or interventions can be established and tested under priority topic Interventions (page 62).

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Surveillance

Standardisation and extension of surveillance systems to establish a global surveillance programme on antibiotic resistance and antibiotic use

The overarching goal of this priority topic is to standardise, improve and extend surveillance systems on antibiotic use and on AMR (in humans, animals, food, and the larger environment) with the final aim to foster a global surveillance system for AMR.

Introduction to problem definition

Once novel mechanisms of AMR have emerged, human travel and migration and the transport of food and animals play a pivotal role in disseminating the genetic elements that are responsible for AMR and/or bacterial clones around the world. For example, important clones of antibiotic-resistant pathogens, such as healthcare-associated Methicillin-resistant *Staphylococcus aureus* (MRSA), originated in Europe or the USA (ST239, ST5) before spreading to Asian and Latin American hospitals. Livestock-associated (LA-MRSA, ST398) *S. aureus* strains emerged in China as a fully susceptible human coloniser, but then turned into a successful MRSA in European pigs. LA-MRSA was subsequently re-imported into China through the international food trade. These recent developments illustrate that bacterial populations are truly global players.

Surveillance networks are essential to monitor the threat of AMR and guide public health policy. In order to understand antibiotic resistance, we must understand whether resistance genes are highly mobile and whether dominant pathogenic clones spread resistance globally. For too long, our response to epidemics of antibiotic-resistant bacteria has been reactive rather than proactive due to the paucity of crucial surveillance data that could have forewarned of the emergence and initial spread of these antibiotic-resistant clones of nosocomial pathogens. Surveillance data will quantify the burden of

resistance, can serve as a warning system and should guide policy makers to develop procedures targeting the most pressing concerns and transmission routes of AMR. Surveillance also has an important role in the detection, and subsequent control, of localised outbreaks in hospital settings. Furthermore, concerted surveillance efforts will increase the ability to document the impact of (bundles of) interventions aimed at reducing the threat of AMR.

Countries have different levels of surveillance and many lack national reporting systems. Moreover, the currently available national and international surveillance programmes are not necessarily set up to meet the needs and expectations of policy makers, professionals and researchers. For example, existing surveillance programmes on AMR are sub-optimal because they lack molecular and genotyping analysis and/or information on patient outcomes. Another obstacle is the absence of a common surveillance reporting system to allow the integration of data from different surveillance systems. There is also a lack of data on the burden of AMR in terms of morbidity and mortality, the economic cost, and the association between the emergence of resistance in humans and in animals and beyond. Furthermore, most data are based on hospital patients and on a limited number of pathogens.
In addition, the antibiotics that are used in the community, in hospitals, in agricultural settings and elsewhere, are the driving forces that will lead to the emergence, selection and spread of novel antibiotic resistance mechanisms and antibiotic-resistant bacteria. Therefore, it is of major importance to not only collect data on AMR, but also on the global use of antibiotics, which will lead to an integrated interpretation of both antibiotic use and the burden of AMR in different sectors (e.g. in hospitals, in community settings, and in agriculture) around the world.

On a global level, we do not yet know from where resistance emerges, nor in which direction AMR will spread (both among bacteria and between countries) or how long it will take to establish itself. Since most new antibiotic resistance mechanisms develop outside Europe, a strictly European surveillance system alone is not sufficient. Globalisation has brought us many advantages but can also greatly speed up the spread of resistance around the world. One of the most worrying recent developments in is the rapid rise of medical tourism of EU citizens to non-EU countries where patients may be colonised or infected with antibiotic-resistant bacterial strains that are rare or absent in their homeland.
In addition, international trade of foods and migration patterns may also contribute to the introduction of novel AMR mechanisms in Europe. Therefore, we require a warning system that will guarantee early detection of pathogens displaying new resistance patterns, in humans, animals or the environment.

Early detection of increasing regional or local accumulations or elevated incidences of certain resistant pathogens is also necessary as these events serve as warning signals that a successful resistant clone may have emerged. Many countries around the world lack either the facilities or the know-how to do state-of-the-art microbiological diagnostics and/or antibiotic sensitivity testing, despite the efforts by the WHO to highlight this area as a priority. By initiating, educating and developing surveillance programmes in these countries, principally through established networks, it is possible to aid patient care and minimise the emergence and spread of resistance. As of 2013, there is no robust global system that truly detects and describes evolving antibiotic resistance mechanisms of importance to humans.

Opportunities

Standardised and extended mapping[L] of AMR will enable us to answer questions related to the magnitude of antibiotic-resistant bacteria as a health problem, as well as on the incidence and mortality attributable to infections with these resistant pathogens. International long-term monitoring of antibiotic use and antibiotic-resistant bacteria will allow the accurate assessment of the impact of policy measures that are aimed at minimising antibiotic misuse and the emergence and spread of antibiotic resistance.

A global AMR surveillance network – covering both developed and developing countries – would allow the perception of a united front against the threat of antibiotic resistance. In addition, global monitoring of antibiotic use will encourage participating countries to adopt regulations to control the overuse of antibiotics. These surveillance activities will give credence to the idea that antibiotic resistance 'is everybody's problem' and that 'we are all in this together'. Surveillance activities should also include data collection on the prevalence of antibiotic-resistant bacteria among healthy individuals and animals, as this will enable us to gauge the size of the reservoir of antibiotic-resistant bacteria outside the hospital environment and may clarify the extent to which agricultural and environmental sources of resistant bacteria contribute to the burden of infections caused by antibiotic-resistant bacteria in humans. A warning system could also provide additional information on the link between the new resistance and pathogenicity and how quickly this resistance can spread throughout bacterial populations. This information is pertinent to the development of new antibiotics and in refining infection control measures. The Technical Assistance and Information Exchange instrument (TAIEX) of the European Commission may be a valuable platform to develop pilot studies to test the feasability of coordinated AMR surveillance in the regions that border the EU. The experiences from the Antibiotic Resistance Surveillance and Control in the Mediterranean Region (ARMed) programme indicate that a surveillance programme outside the borders of the EU is feasible and will provides important insights into the spread of AMR in these regions [25].

In December 2012, the WHO held a consultation on strategies for global AMR surveillance, which defines the basic elements for a roadmap on AMR surveillance. Collaboration with the WHO, but also with the FAO and the OIE is necessary to improve current national and international surveillance systems and to make the establishment of a global surveillance programme – with many policy challenges– feasible. Current publicly driven European surveillance systems such as EARS-Net on resistance in hospitalised patients (ECDC) and the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) on the use of antibiotics in agriculture could be used as blueprints, which can be extended in terms of international coverage, scope of genetic data and patient outcome.

There are clear synergies between the results of this research topic and the aims of other priority topics within the SRA. The surveillance data will aid future drug design (topic Therapeutics, page 37) and help to develop specialised interventions (page 57). Data from this topic will also provide information on global hot spots of new resistant clones that can be scrutinised more closely within priority topic

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[L]   To determine the occurrence (incidence or prevalence) of the burden of disease.

Transmission dynamics (page 42). Information from this topic will provide knowledge regarding the role of the environment and human normal flora in maintaining resistant clones and thus on indicators to be modelled and analysed in priority topic Environment (page 57). Finally, the development of diagnostic tools (page 42) could make the different surveillance aims more achievable and may importantly reduce the cost of surveillance programmes. It is important to realise that a good research infrastructure to introduce state-of-the-art diagnostic tools and more robust solutions is necessary, but is currently often lacking, particularly in low and middle-income countries.

Research objectives and activities

Operational research on the standardisation and extension of surveillance systems

In collaboration with the WHO, the strengths and weaknesses of the (inter)national antibiotic resistance surveillance networks of individual countries, both in Europe and beyond, have to be identified along with regions of excellence that can act as hubs for knowledge dissemination. In parallel, the needs of different stakeholders regarding surveillance data need to be thoroughly explored. This exercise should identify the resources and needs for a standardized surveillance system for AMR and should provide a step-by-step overview of actions that need to be taken in order to standardise, improve and extend currently available surveillance system. Furthermore education and behavioural interventions are also fundamental to good management aimed at curtailing antibiotic resistance at a local and national level.

Pilot study regarding a global surveillance programme

Based on the outcome of the methodological assessment and optimisation of existing surveillance systems, a pilot study into the implementation of a phenotypic and genotypic global surveillance programme on antibiotic resistance in patients, both in hospital and in the community, and healthy people, as well as livestock is required. In this study, the logistical feasibility of a global surveillance programme will be examined in order to provide realistic future costing models. Surveillance should include both phenotypic and genotypic analyses, specifically of bacterial clones associated with antibiotic resistance genes, mechanisms of resistance and association of resistance genes with mobile genetic elements. Local demographic data should include local patient outcome to correlate risk factors associated with infection. Genotypic data should provide information on the relatedness of antibiotic-resistant bacteria, antibiotic resistance genes and the elements that carry these genes. A global antibiotic surveillance programme, in partnership with the WHO, must encourage national auditing and international participation through the establishment of sub-committees comprised of world-class specialists to deliver global recommendations and guidelines on susceptibility testing and genotyping of bacterial strains.

In the pilot project, a defined set of pathogens and resistance markers that are a global priority need to be identified and international capabilities of sampling-methods and transport need to be explored. New technologies that will address both phenotypic and genotypic analysis of key pathogens in countries with limited capacities and capabilities need to be surveyed and implemented. State-of-the-art technologies will include strain typing and genomic sequencing, which should be performed in recognised centres with appropriate expertise. Finally, an international quality control programme to

encourage good governance at both phenotypic and genotypic levels should be implemented. This requires the establishment of online forums, management committees, and comprehensive international databases. There must also be close cooperation with the WHO, FAO, and the OIE, in aiding global antibiotic resistance by means of awareness campaigns. Once the pilot study has been implemented, delivered and assessed, a long-term world-wide programme could be initiated.

Surveillance on antibiotic use

Besides assaying for resistance, more information needs to be collected on the global usage of antibiotics in humans, agriculture and aquaculture. Even in regions like the EU and the USA, with comparatively better health-monitoring systems than developing regions, prevalence of antibiotic use is difficult to accurately measure, although researchers are attempting to do so. Collaborative efforts between public bodies and the pharmaceutical industry to gauge the global usage of antibiotics in different regions need to be developed in order to accurately estimate usage of antibiotics worldwide.

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Transmission
Transmission dynamics

The overarching goal of this priority topic is to establish multidisciplinary research networks to investigate the dynamics of transmission and selection of AMR at the genetic, bacterial, animal, human, societal and environmental levels, in order to design and evaluate preventive measures for controlling resistance.

Introduction to problem definition

An organism develops resistance either by gene mutation or by the acquisition of genetic components from another strain. Without transmission, resistance would remain an isolated problem. However, selection and transmission lead to the amplification of resistance and turn it into a major public health problem.

Selection and transmission are two different phenomena. Selection by itself (due to the consumption of antibiotics and other biocides and subsequent release of antibiotics and/or antibiotic-resistant bacteria into the environment) can explain only in part the increase in antibiotic-resistant bacteria, indicating that transmission is also crucially important.

Selectors (such as antibiotics, disinfectants, and heavy metals) kill or inhibit the growth of susceptible strains, thus providing an evolutionary advantage to resistant strains. Selectors may not only have significant effects on selection, but also on transmission because transmission of resistance is far more likely to occur under pressure from a selector. However, selectors may also differentially affect bacterial species and mechanisms of resistance. These effects of selectors may even vary in the different compartments of the human body, due to differences in the levels of exposure, competing flora, and host immune factors. For example, an antibiotic given intravenously and which reaches high levels in the lung and cures a lung infection, may reach only low levels in the gastrointestinal tract. However, even these low levels of antibiotics may still select for antibiotic-resistant bacteria in this compartment. This may still have a considerable effect on the emergence and spread of antibiotic

resistance as the gastrointestinal tract is the main body site where selection for resistance occurs, and in which resistance genes are exchanged between organisms resulting in new resistant clones. The gut also serves as the main reservoir for resistance from which transmission to others occurs due to fecal contamination.

Targeting the determinants that contribute to the spread of antibiotic resistance genes and antibiotic-resistant bacteria may become highly relevant given the current lack of successful pharmacological interventions (such as antibiotics and vaccines). For instance, on the genetic level, selectors may induce the transfer of genetic material by transformation (the uptake of DNA fragments by bacteria), conjugation (direct transfer of DNA between two bacteria through a sex pilus), and transduction (transfer of DNA mediated by bacteriophages), between bacterial populations resulting in new resistant clones. On the population level, frequency and duration of hospital admission and the volume of patient traffic between healthcare institutions, as well as transport of farm animals and the complex dynamics of the modern food chain, also contribute to dissemination of AMR. It has become evident that certain bacterial strains are particularly successful in transmission within and between healthcare settings.

Transmission of resistance and selection for resistance occur at various levels (figure 2, page 20):
- Transmission of genetic elements encoding antibiotic resistance within and between bacterial species and selection of resistant strains and genetic resistance elements.
- Dissemination by transmission of resistant strains and successful clones between individuals, and selection of these strains by antibiotics and other selectors.
- Selection of resistance in non-human reservoirs and transmission between human and non-human reservoirs and vice versa.
- Transmission at the human population level, between hospital wards, between community and hospitals, acute-care and long-term care institutions, and between healthcare settings in different countries.

To understand the complex biological system that shapes the spread of antibiotic resistance, multiple disciplines need to work together, according to the One Health concept, to identify and characterise the determinants that contribute to the spread of resistance in and between different reservoirs; including livestock, and both sick and healthy people. It is of particular interest to gauge the contribution of the large veterinary reservoir of antibiotic-resistant bacteria to resistance in humans and the role that food may have in transferring resistance genes and antibiotic-resistant bacteria from animals to humans. This is a topic of considerable debate but few studies have been done to allow inferences of causality and directionality of spread of resistance genes between human and animal reservoirs.

Understanding the complex biology and epidemiology of selection and transmission of resistance is crucial in order to design preventive measures aimed at curtailing this public-health threat. Therefore, detailed epidemiological studies measuring the effects of selectors on selection and transmission at all levels and examining the status of the host and the specific microenvironment and ecology are required. Testable interventions following on from these studies will be scientifically evaluated in research topic Interventions (page 62).

Opportunities

This research priority offers an opportunity to understand the complexity of how resistance is spread. It aims to identify critical control points at which interventions could substantially affect the spread of resistance. For example, efforts to control the transmission of ESBL[M] have focused on hospital interventions. However, recent studies have suggested that transmission of ESBL-producing *E. coli* also occurs in the community, possibly through the food chain. Thus efforts should be directed at quantifying the importance of food, particularly of meat products, as a vehicle for resistance genes and resistant bacteria. The dynamics of resistance genes in the microbiota of humans and animals also need to be studied as it is of crucial importance to understand how these genes can spread between the different bacteria of the gut microbiota and to determine the extent to which the mobile elements that carry resistance genes are retained in the microbiota in the absence of selection. Studies on these important aspects of transmission of antibiotic resistance should take advantage of novel single cell tools and high throughput DNA sequencing.

The knowledge gained by the proposed research activities will lead to recommendations to optimise the use of antibiotics to maximise their benefits to the individual patient and minimise the ecological harm to society. It will allow interventions aimed at the interaction between genetics, bacteria and humans, between human and non-human reservoirs, and between regional, national and international patient networks. For example, previous outbreak investigations identified the animal use of avoparcin[N] as a growth promoter as an important selector of vancomycin-resistant enterococci (VRE) in the community in Europe. The examples of spread of ESBL-producing *E. coli* and VRE show how understanding transmission may have a profound impact on the measures that can be taken to limit the spread of these resistant bacteria.

Indeed, the basis of any outbreak investigation is to understand the natural history and chain of events, and intervening at the critical points. Selection and transmission should be studied comprehensively at the different levels, from the gene to the bacteria, to the individual patient, to the hospital setting. In addition, insights should be gathered into the role of agriculture and the food chain in transferring antibiotic resistance from different reservoirs to humans. A relatively understudied subject in the spread of antibiotic resistance is the assessment of the impact of international networks of health care in which patients are shuttled between different health-care providers. The assembly of a European HealthCare Utilisation Atlas may provide guidance for policy decisions and an objective assessment of the influence of the EU directive of patient rights to cross-border health care. It will also be possible to appraise the role of primary health care (GPs or family doctors) as gatekeepers to hospital admissions. Inherent to this analysis is the mapping of the distribution of clones and plasmids with particular public health importance, which will generate the contextual evidence for the association between healthcare networks and the abundance of certain genomic lineages of important nosocomial pathogens. The superimposition of data concerning effects of selectors on the bacterial level, with local and global

[M] Extended Spectrum Beta Lactamases (ESBL's) are enzymes that are made by bacteria and makes them resistant against almost all kind of beta-lactam antibiotics.

[N] Avoparcin is an antibiotic that is active against gram-positive bacteria. Chemically, it is highly similar to another antibiotic, vancomycin, which is used in the treatment of infections that are caused by Gram-positive bacteria. Because avoparcin and vancomycin are nearly identical, the the use of avoparcin has led to an increase in the resistance for vancomycin in animal-related enterococci.

distribution of successful bacterial clones and with different healthcare delivery systems will provide a highly innovative way of providing contextual evidence for the association between healthcare networks and bacterial evolutionary networks. Such evidence will offer a comprehensive understanding of the dynamics of the spread of antibiotic resistance and how this spread can be efficiently curtailed. Minimising the spread of AMR will greatly benefit public health as it will contribute to the control of antibiotic-resistant infections in community and health-care settings, and in agriculture.

The knowledge gained by research in this priority topic will be incorporated into the design of new antimicrobial agents and disinfectants to reduce their collateral damage (topic Therapeutics, page 37) and in future clinical trials to assure cost-effective prevention of antibiotic resistance transmission (topic Interventions, page 62).

Research objectives and activities

Unravel the complex dynamics of selection and transmission of antibiotic resistance

Multidisciplinary research networks are needed to conduct collaborative and complementary studies that will unravel the complex dynamics of selection and transmission of antibiotic resistance. These studies should provide a better understanding of the mechanisms that contribute to the spread of antibiotic resistance, which will provide testable hypotheses for interventions aimed at controlling the emergence and spread of antibiotic resistance. The execution of the necessary clinical evaluation is part of research topic Interventions (page 62).

Identifying factors for the persistence and spread of resistant organisms and resistance genes

To explain epidemicity of antibiotic-resistant clones, international research consortia are needed that will investigate factors accounting for the success of clones, organisms, and resistance patterns. This should result in identifying events and factors that account for the persistence and spread of resistant organisms and genetic determinants. Selection and transmission between individuals and between human and non-human sources should be studied. Mathematical modelling can be used to determine the success and abundance of antibiotic resistant bacterial strains with particular public health importance through the development of risk assessment approaches that are based on the genomic repertoire of bacterial pathogens and the ecological constraints that determine their fitness in clinical, community and veterinary settings.

Understanding the different systems of health care, animal production and global trade and their impact on AMR

Comparative systems research is needed to understand of the different healthcare systems in EU countries that may facilitate or inhibit the expansion of antibiotic resistance in different European countries as well as the animal production system. In addition, the role of migration, tourism, and agricultural practices (including animal transport) on the dissemination of antibiotic resistance among humans needs to be explored.

Finally, an integration of biological, epidemiological and economic data will identify the important drivers of exposure of humans to antibiotics and antibiotic resistance genes. This information may be translated into policy measures to control the emergence and spread of antibiotic-resistant bacteria in the participating countries.

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Environment

The role of the environment as a source for the selection for and spread of antimicrobial resistance

The overarching goal of this priority topic is to call for the implementation of activities to assess the impact of human activities on the spread of antimicrobial agents, resistance genes, and multi-drug-resistant bacteria to water (both potable water, and water in the environment), food and soils[o]. Insights into the role of the environment in the selection for and spread of antibiotic resistance should lead to the establishment of novel management guidelines and to the development of bio-remediative and bio-restorative interventions (waste management techniques that involves the use of organisms to remove or neutralise antibiotic residues or antibiotic resistance genes from contaminated sites).

Introduction to problem definition

Residues of antibiotics, antibiotic resistance genes and antibiotic-resistant bacteria are excreted via effluents and sewage into the environment. From there they can re-contaminate humans and animals, for example via drinking water, irrigation, soil, or foodstuffs. Recontamination occurs proportionally to the lack of sanitation, as is shown in South Asia where environmental contamination with multi-drug resistant *Enterobacteriaceae* is alarmingly widespread and contributes to high carriage rates of these bacteria among healthy individuals. However, European countries are also affected by the problem, as shown by the spread of methicillin-resistant *Staphylococcus aureus* in pigs and pig

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[o]   Complementary to the transmission studies in topic Transmission dynamics.

farms[P] or in the 2011 foodborne outbreak of a highly virulent, multi-drug resistant *E. coli* O104:H4 strain in Germany[Q].
It has been suggested that ESBL-producing *E. coli*, which may cause life-threatening infections in hospitalised individuals, are recurrently acquired; at least in part, through the food chain.

However, the true quantitative contribution of cross-contamination with antibiotic-resistant bacteria between humans, animals, or in multi-species exchanges via the surrounding environment, including water and the food chain remains undetermined. With increasing global trade, the import of meat and other food products from non-EU countries is expected to rise which increases the possibility of the importation of multi-drug resistant and extensively drug resistant bacteria together with these foodstuffs. Faecal contamination of food and drinking water in developing countries can also be a major factor in the contamination of food. Consequently, effective treatment of both animal and human sewage is critical to prevent such contamination.

Whilst it has been known for some time that enterococci, particularly VRE, has spread from animal reservoirs to humans, the notion that human and animal waste could impact significantly on human health has been particularly strengthened by the emergence of multi-drug resistant *Enterobacteriaceae*. The fact that all humans and animals usually carry *E. coli* as part of their gut flora and that this organism causes the majority of community acquired disease, mainly arising from endogenous sources, demonstrates their significance. Humans and animals may be considered as walking incubators for bacteria as they can carry between 10 and 100 trillion bacteria in and on their bodies, with highest levels being reached in the colon; faeces contains between 10 billion to one trillion bacteria per gram. Thus, the management of human and animal waste is essential in lowering the burden of environmental drug-resistant bacteria that can cause untreatable infections in the community.

In Europe, very little data exists on environmental contamination by antibiotic residues and faecal bacteria, carrying resistance genes, through sewage or run-offs. It is therefore impossible to quantify the contribution of these factors on antibiotic resistance. Nevertheless, EU directives concerning sewage and waste-water treatment have contributed to relatively high water-quality in Europe.
In contrast, in many Asian, African, and South American countries, processing of human and animal waste is currently wholly inadequate. Because of lack of finances, this will remain an urgent concern as national governments often do not see this issue as a priority and may fail to understand the indelible link between sanitation and the containment of human pathogens.

Until now, environmental risk factors for the dissemination of resistant bacteria have not been adequately assessed. Ad-hoc studies have examined the effects of antibiotic contamination on AMR.

[P]   A specific population of methicillin-resistant Staphylococcus aureus (termed LA-MRSA or ST398) was first recognized in pigs and pig-farmers in The Netherlands. These strains are genetically distinct from strains that cause hospital-acquired and community infections.

[Q]   An outbreak of bloody diarrhoea and haemolytic uraemic syndrome (HUS) due to a specific E. coli O104:H4 strain occurred in Germany in May and June 2011. Almost 4,000 people were affected by and 53 died. The source of the infection was linked to the consumption of contaminated sprouts of fenugreek sprouts.

However, these are small point-prevalence surveys and lack the scope to identify risk factors. Food contamination, particularly in relation to environmental contamination, is a critical area that has lacked a systematic analysis. The extent to which food that is produced in the EU, as well as food that is imported into the EU carries antibiotic-resistant bacteria and whether these bacteria may colonise healthy individuals through the preparation and consumption of the food is currently unknown. In addition, it is as yet unclear how current practices in food production (e.g. in slaughterhouses, but also the use of heavy metals, disinfectants and biocides during food production) could contribute to the selection and spread of AMR.

Although water decontamination treatments are being piloted in areas lacking sanitation, there is not a systematic publicly funded programme that addresses the impact of sewage (and sewage treatment) on resistance in the environment, animals, food contamination, and potable water. Reducing bacterial load, particularly of high-risk resistant clones, or inactivating the genetic determinants that are involved in the propagation of resistance genes in the environment should significantly lessen the burden of multi-drug-resistant bacteria in communities and, by extension, hospitals, and thereby reduce the impact of AMR on public health in developing countries.

Opportunities

The main goal in this topic is to investigate methods to quantify and reduce the burden of antibiotic resistance in the environment. In particular, the entry, persistence, and dissemination of human- and animal-based bacteria into the soil and drinking water needs to be addressed, since the environment is a key hub in the spread of antibiotic resistance. Research on the way that water and sewage can be decontaminated to avoid antibiotic resistance remains extremely scarce. This topic will contribute to fill this critical gap.

An initial activity could be to undertake a comprehensive human health risk-assessment of the burden associated with AMR in the environment. Not only will this add AMR to the list of health risks that are associated with environmental changes and pollution, but it will provide robust evidence for decision makers and policy managers to address these issues. Secondly, research within this topic could lead to the elucidation of the complex interplay between the three major components (antibiotic residues, naturally resistant bacteria, and those with acquired resistance mechanisms) that make the environment of major importance in contributing to the global burden of AMR. Insights in this field may help to identify new opportunities for the control of the emergence and spread of AMR. Thirdly, innovative solutions to control the phenomenon at the individual and collective levels may be stimulated. Currently, there are a number of technologies which are used to treat waste-water. However, these technologies do not necessarily address the issue of whether residues of antibiotics and populations of antibiotic-resistant bacteria can be decontaminated, particularly from hospital or farm effluents. Consequently, the merits of different wastewater treatment technologies and whether they can be used to minimise levels of antibiotic residues and antibiotic-resistant bacteria need to be explored.

The development of these innovations would not only result in better control of AMR in terms of individual and public health, but would also generate economic activities that would be beneficial to Europe. Developing countries will need novel low-tech procedures for wastewater decontamination; currently, there is very little international collaboration on this issue. This topic, along with the JPI AMR in general, creates a good opportunity to strengthen initiatives (such as ERA-ENVHEALTH) in this field and to create more synergy between them. This topic could also benefit from experiences gained in the general field of sustainable development as AMR is conceptually linked to other initiatives that aim to safeguard important resources for future generations.

This priority topic will provide a global ecological and eco-genetic framework that is highly synergistic with the objectives of priority topic Transmission (page 52) which focuses more specifically on the transmission of specific clones. In addition, the surveillance activities that are proposed in topic Surveillance (page 47) may be used to gauge whether improved sanitation in developing countries will lead to a reduction in carriage rates of antibiotic-resistant bacteria in healthy individuals. Development of standardised testing for the quantification of antibiotic-resistant bacteria may also be done in conjunction with the research proposed in the same priority topic (page 47).

Research objectives and activities

This topic will evaluate the risk, for human and animal health, of environmental pollution with residues of antibiotics and antibiotic-resistant bacteria.

Identification of interventions that reduce the burden of AMR in the environment

The first research efforts (covering short-term goals) within this area need to focus on the identification of interventions that may reduce the burden of AMR in the environment. A meta-analysis of national and international strategies for waste disposal and its relation to the spread of antibiotic-resistant organisms among people and animals is needed. Country-wide studies are needed to explore concentrations of antibiotics and heavy metals, which are risk factors for multidrug-resistant bacteria, in wastewater and how these are affected by current sewage treatment approaches. In addition, the levels of environmental contamination with antibiotics (and other selective agents such as biocides and heavy metals) that will lead to selection for resistance is unknown.

Risk assessment to estimate key environmental transmission pathways

A risk assessment is needed to aid decision makers in estimating which of the various transmission pathways from the environment to humans is the most important to address in order to focus additional efforts to reduce the burden of AMR in the environment on relevant vectors. Examples of transmission pathways include water, soil, air, food, livestock, and companion animals.

Understanding the basic biological processes

More basic research is need to define the extent of the burden of AMR in the environment, which includes the evaluation of existing methods, and the development of novel methods and protocols to assess the presence of antibiotics, resistance genes, and resistant bacteria in the environment.

Development of industrial systems to reduce AMR in the environment

Applied research could stimulate the development of industrial systems to reduce AMR in the environment. Such methods could include: (a) the development of methods that reduce the excretion via faeces or urine of antibiotics and antibiotic-residues in treated humans and animals, and (b) the development of novel bio-engineering methods to minimise the release and spread of AMR in the environment. Finally, sewage and waste-water treatment needs to be evaluated in terms of their effect on the reduction of the environmental concentration of antimicrobials and antibiotic-resistance genes, vectors and resistant bacterial organisms.

Over five to ten years, the results of the above research will lead to an accumulation of knowledge on about the exact role of each type of environment in terms of risk for the selection and dissemination of AMR and an understanding of the basic biological processes that underlie these phenomena. Most importantly, new industrial methods to decrease additional pollution of the environment by resistant bacteria and antibiotic residues, and reduce the antibiotic residues that already contaminate the environment, need to be developed by the European bio-sanitation engineering industry.

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PRIORITY TOPIC

F

Interventions

Designing and testing interventions to prevent acquisition, transmission and infection caused by AMR

The goal of this topic is to launch research projects to support and conduct controlled studies that evaluate evidence-based strategies. These strategies will aim to control resistance, and reduce the risk of acquisition, transmission, and infection by antibiotic-resistant pathogens in hospitalised patients, outpatients, healthy people, animals, and the environment.

Introduction to problem definition

An important challenge will be prolonging the usefulness of existing antibiotics by minimising their misuse in clinical medicine, and in veterinary, and food-production settings. Furthermore, interventions are needed to prevent the acquisition, transmission and infection of antibiotic-resistant bacteria by modifying the exposure of individuals or populations.

To develop cost-effective interventions, knowledge about the acquisition, occurrence, transmission pathways of AMR on different levels among other aspects is needed. The EU has significantly invested in biomedical research on resistance, yet little of this research has been translated into interventions to significantly improve health care. The reason for this is that most of the funded research has been of an observational and descriptive nature: for instance, to understand the molecular mechanisms of novel antibiotic-resistant bacteria. While such basic research is crucial in understanding how resistance can evolve, it does not directly inform prevention and control strategies. Furthermore, much of what has been recommended as interventions to control AMR over the past two decades has been based on experience, empiricism, and common sense; rather than on strong evidence. Consequently, the evidence-base for interventions to prevent acquisition, transmission and infection caused by antibiotic-resistant bacteria remains weak for many key interventions including detection, screening,

isolation, decolonisation, environmental decontamination, and antibiotic stewardship. Often, such approaches seem rational only on the basis of limited scientific evidence from poorly controlled studies. This evidence base remains inadequate to support the mandatory implementation of many of these interventions or to guide the manner of their implementation.

This lack of an evidence-base is a problem in veterinary science too, which has few prospects for new antibiotics and therefore, interventions such as lowering antibiotic usage in animal husbandry are vital. For example, a promising intervention focuses on lowering the antibiotic usage in animal husbandry. Recent research indicates that reducing antibiotic usage need not threaten food production or economic profitability. In addition, interventions that are aimed at improving the living conditions of livestock may also prevent infectious diseases in large flocks and herds, thereby reducing the need for antibiotics. However, more information is needed on the way that approaches to reduce antibiotic usage in animals in different EU countries and livestock populations will impact on economic costs, animal welfare and development of resistance, through antibiotic-reduction programmes in different EU countries and different livestock populations.

It is a formidable challenge to decrease the misuse of antibiotics as well as to implement measures to block transmission of AMR in humans and animals. Cultural, contextual, and behavioural determinants influence antibiotic use and may also determine whether interventions to improve antibiotic use and/ or behaviour (such as hand hygiene) can be successfully implemented. Since the determinants that contribute to the misuse of antibiotics or non-compliance with guidelines can be diverse, the strategies to tackle them need to be equally diverse.

In summary, controlled integrated studies in society, health care, and agricultural settings are urgently needed to devise the optimal intervention strategies to prevent acquisition, transmission, and infection caused by antibiotic-resistant bacteria in humans and animals. Such studies could include trials to test multimodal infection-control interventions and various strategies that should be aimed at improving antibiotic stewardship.

Opportunities

Research into interventions and implementation strategies is likely to be important for physicians and other health-care workers, veterinarians, epidemiologists, and policy makers in establishing recommendations for national and international antibiotic resistance control guidelines. Assessment of the usefulness and cost-effectiveness of new recommendations should be of value for those in charge of infection control and antibiotic stewardship in both healthcare and veterinary settings. Ultimately, this research will contribute to the prevention of antibiotic-resistant infections and improved quality of patient care and safety in Europe.

This research priority offers many important starting points for future research activities and technical innovations, which could be useful for those in industry, healthcare management, and health insurance companies. New technologies may arise from studies that provide incentives for companies to develop more sophisticated and evidence-based decontamination protocols, for example using UV-light or vaporised hydrogen peroxide, in hospitals or farms. The assessment of strategies to guide behavioural changes that modify perceptions and compliance of healthcare workers with respect to

hygiene precautions will enhance opportunities to design new electronic monitoring devices that detect when healthcare workers have contact with patients and then remind them to use disinfectant hand rubs. All these approaches could offer cost-effective solutions to a pressing need in health care.

Insights on the acquisition and transmission of AMR and the strategies that were developed based on these insights (topic (page 52) and topic (page 57) can be developed into interventions with an implementation strategy, and tested for its cost effectiveness. Surveillance data (page 47) and the risk assessment of different transmission pathways (page 52 and page 57) can be used to determine areas of concern and prioritisation on further development and testing of interventions in specific areas. The knowledge that is generated by research into this topic can be used to optimise the development and implementation of novel antibiotics and alternatives to antibiotics (page 37). Implementation strategies and research will also be needed to improve the use of current diagnostics tools and implement novel diagnostic tools (page 42).

Research objectives and activities

Research into effectiveness of AMR prevention and control strategies

Carefully designed multi-centre prospective intervention trials are needed to establish the effectiveness of AMR prevention and control strategies. Therefore, high-quality, multi-centre studies are needed to focus on different aspects of prevention, diagnosis, and treatment of antibiotic-resistant infections. For these studies, randomised clinical trials are a sub-optimal design, as these trials are specifically meant to evaluate novel drugs or products. Instead, cluster-randomised studies, in which groups of individuals are randomly allocated to interventions, have emerged as a useful and credible design to study interventions, although they require significant resources and the gathering of a broad partnership of institutions and investigators to yield useful results. Cluster-randomised studies that involve a large, heterogeneous set of hospitals, healthy humans, or agricultural settings and are independent from single pharmaceutical companies may yield more generalisable and clinically relevant results than a randomised trial in a single location. The potential directions of such ambitious research trials and interventional cohort studies are outlined below.

Comparing and combining AMR prevention and control practices

Cost-efficacy trials need to be identify which prevention methods are most effective in different settings. For example, it remains highly controversial whether the screening of patients and precautions on contact between people are necessary to control the spread of ESBL-producing *Escherichia coli* in healthcare settings. Separate, simple, infection-control measures (such as hand hygiene and patient isolation) are frequently performed collectively, in so-called 'bundles'. Multi-modal implementation studies of these infection control bundles, including antibiotic stewardship, need to be performed so that their effects in preventing the emergence and spread of resistant organisms can be determined.

Real-world implementation

Special emphasis should be placed on methods to inform and involve patients and farmers as well as prescribers about the threats related to AMR and their role in the fight against AMR. There have been numerous campaigns to promote appropriate use of antibiotics in high-income countries, varying

from simple, low-cost internet campaigns to expensive mass-media campaigns. The capacity of these campaigns to effect behavioural change, and how these affect the development of resistance to antimicrobial drugs is difficult to assess. The multifaceted approach of those campaigns, simultaneously targeting physicians, veterinarians and the general public with multiple interventions, makes it difficult to establish which strategy is most efficient in changing attitudes and practices. Thus, further research is needed, particularly in low- and middle-income countries where usage of antibiotics is poorly controlled.

A promising strategy for new interventions is to target the logistics of care in the context of antibiotic use, and the communication and collaboration between healthcare professionals. Specifically, it remains unclear to what extent computerised decision support systems may help to improve antibiotic prescription, and how these systems could influence the emergence of resistance.

Real-world implementation of best practices, using quality-improvement methods or clinical algorithm testing strategies (e.g. small-scale interventions to prevent hospital- or animal husbandry-acquired infections by multidrug-resistant microorganisms), need to be evaluated. Cross-sectional surveys to assess the quality and effects of implementation strategies (such as education, role models) on minimizing unnecessary antibiotic treatment in various settings and countries are required. This is necessary because it remains unclear to what extent the heterogeneity of culture, healthcare systems, agricultural practices, consumption of antibiotics, and resistance to antibiotics across European countries warrants different implementation approaches. It will also be important to better understand (and, ultimately, to take action) of the possible causes of why previous implementations have failed. These macro-epidemiological and sociological studies will complement the intervention studies that are proposed in this priority topic.

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Appendices

Appendix I
Development process of the Strategic Research Agenda

Development process of the Strategic Research Agenda
A first workshop was held in May 2011 to identify the major needs and challenges from a scientific perspective. After this workshop, JPI has established a Scientific Advisory Board to further develop these needs and challenges into a Strategic Research Agenda. In 2013, a Stakeholder Advisory Board was also established to deliver input on the agenda. Below are the key elements of the process:

– Five meetings of the Scientific Advisory Board (first meeting in 2011, second meeting in 2012, and four more meetings in 2013)
– A consultation process with stakeholders:
– Stakeholder Advisory Board meetings: Discussion of the SRA 1st draft in Brussels 18th April 2013 (*more meetings are scheduled*)
– A stakeholders workshop: Geneva Invitation Conference 27th and 28th of May 2013 with members of the Management Board, Scientific Advisory Board, Stakeholder Advisory Board and 7 additional experts discussed a 2nd draft of the SRA
– A series of expert workshops:
– Preliminary workshops in 2012
– Workshop on veterinarian perspective of AMR on 31st of July 2013
– Brainstorming workshop with AMR experts at the July 2013 FEMS Conference in Berlin
– An online public consultation process (1st September – 15 October 2013)
– 44 questionnaires
– 11 national advices of participating countries

The SRA adoption took place in the JPIAMR Management Board in December 2013. The SRA is scheduled to be launched in April 2014.

Members of the Scientific Advisory Board
Chair: Herman Goossens, University of Antwerp, Belgium
– Antoine Andremont, Bichat-Claude Bernard Hospital, Paris, France
– Fernando Baquero, IRYCIS, Madrid, Spain
– Marc Bonten, UMC Utrecht, div. Julius Centrum, Utrecht, The Netherlands
– Yehuda Carmeli, Harvard University, Boston, United States of America
– Petra Gastmeier, Institute for Hygiene and Environmental Medicine, Berlin, Germany (since October 2013)
– Niels Frimodt-Møller, Statens Serum insitut, Copenhagen, Denmark
– Bruno Gonzalez-Zorn, Complutense University, Madrid, Spain
– Hajo Grundmann, UMCG, Groningen, The Netherlands
– Stephan Harbarth, Hôpitaux Universitaires de Genève, Switzerland
– Birgitta Henriques Normark, Karolinska Institutet, Stockholm, Sweden
– Patrice Nordmann, Hôspital de Bicêtre, Paris, France (until September 2013)
– Arnfinn Sundsfjord, University of Tromsø, Norway
– Timothy Walsh, Cardiff University, Cardiff, United Kingdom
– Paul Williams, University of Nottingham, United Kingdom

Organisation/secretariat
- Willem van Schaik, UMC Utrecht/ ZonMw, the Netherlands
- Jolien Wenink, ZonMw, the Netherlands

Members of the Stakeholder Advisory Board
- Action on Antibiotic Resistance (ReAct)
- European Federation of Pharmaceutical Industries Associations (EFPIA)
- Federation of European Microbiological Societies (FEMS)
- Federation of Veterinarians of Europe (FVE)
- Standing Committee of European Doctors (CPME)
- World Health Organization – Regional Office for Europe (WHO)
- European Centre for Disease Prevention and Control (ECDC)
- European Medicines Agency (EMA)
- European Patient's Forum (EPF)
- European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
- European Food Safety Authority (EFSA)

Consulted additional experts
SAB meeting January 2013
- Jos van der Meer, Radboud University Nijmegen, the Netherlands
- Jürgen Heesemann, Ludwig-Maximilians-Universität München, Germany

Invitational conference Geneva 27-28 May 2013
- Friedrich, Götz, Tübingen Univerity, Germany
- Ingrid Smith, Haukeland University Hospital, Norway
- Sesin Kocagoz, Acıbadem Üniversitesi School of Medicine, Turkey
- Greet Vos, Erasmus MC, the Netherlands
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- Jan Vaarten, Federation of Veterinarians of Europe, Belgium
- Jaap Wagenaar, Utrecht University, the Netherlands
- Dariusz Wasyl, National Veterinary Research Institute, Poland

Appendix II
Abbreviations

AMR	Antimicrobial Resistance
CSA	Coordination & Support Action
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ESBL	Extended Spectrum Beta Lactamases
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
FAO	Food and Agriculture Organization of the United Nations
FDA	US Food and Drug Administration
IMI	Innovative Medicines Initiative
IPR	Intellectual Property Rights
JPI	Joint Programming Initiative
MRSA	Methicillin-resistant *Staphylococcus aureus*
NDM-1	Metallo-beta-lactamase-1
OECD	Organization of Economic Co-operation and Development
OIE	World Organisation for Animal Health
PKPD	Pharmacokinetic/pharmacodynamic
PPP	Public-Private Partnerships
SOP	Standard Operating Procedure
SRA	Strategic Research Agenda
TAIEX	Technical Assistance and Information Exchange instrument
VRE	Vancomycin-resistant Enterococci
WHO	World Health Organization

Appendix III
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Appendix IV
Member States and their representing organisations

Belgium	Dept. Economy, Science and Innovation, Flemish Government
Canada	Canadian Institutes of Health Research (CIHR)
Czech Republic	National Institute on Public Health (NIPH)
Denmark	The Danish Council for Strategic Research
Finland	Academy of Finland
France	National Agency for Research (ANR), INSERM
Germany	Forschungszentrum Jülich GmbH
Greece	General Secretariat for Research and Technology
Israel	Ministry of Health
Italy	Institute of Health
The Netherlands	ZonMw
Norway	Ministry of Health and Care Services
Poland	National Medicines Institute
Romania	National Authorithy for Scientific Research
Spain	Instituto de Salud Carlos III
Sweden	Swedish Research Council
Switzerland	Federal Department of Economic Affairs
Turkey	The Scientific and Technological Research Council of Turkey (TÜBITAK)
United Kingdom	Medical Research Council

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