

Joint Programming Initiative on Antimicrobial Resistance

Strategic Research and Innovation Agenda on Antimicrobial Resistance

Version 2021



Joint Programming Initiative on
Antimicrobial Resistance, JPIAMR

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Executive Summary

The Joint Programming Initiative on Antimicrobial Resistance

The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) ¹ is an international collaborative platform coordinating and funding research on antimicrobial resistance (AMR). JPIAMR facilitates alignment of research programmes between member countries, as well as initiating and coordinating international funding initiatives on AMR through its Strategic Research and Innovation Agenda (SRIA). Through implementation of the SRIA, the JPIAMR supports research on the development of new therapies, stewardship of new and existing antimicrobials, and strategies to monitor and prevent the spread of AMR between humans, animals, and the environment in a One Health² perspective, with the overall goal to decrease the burden of AMR. The SRIA defines six priority topics through which coordinated research activities are translated into new and/or improved strategies to address AMR.

The JPIAMR goals are:

- To align national and international research programmes.
- To support and coordinate transformative research.
- To develop the JPIAMR-Virtual Research Institute.
- To promote innovation and translation of research results.
- To bridge the gap between research and policy.

Strategic Research and Innovation Agenda

The SRIA is an update of the JPIAMR Strategic Research Agenda (SRA) that was published in 2014. The original document has provided a research framework for JPIAMR joint actions to date, outlined key areas of AMR that should be addressed, and provided guidance for countries to align their AMR research agendas nationally and internationally. The SRA adopted the One Health approach and is included in the Global Action Plan on Antimicrobial Resistance (WHO, 2015) as a recommendation for national AMR research plans.

The JPIAMR SRA formed the basis for the strategic approach of alignment taken by JPIAMR member countries to modify their national programmes, priorities or activities and the adoption of joint research priorities in the context of Joint Programming. The JPIAMR SRA is referenced in many national plans with regards to the research elements that should be prioritised and addressed to improve the efficiency of investment in research at the level of individual countries, the European Research Area, and through international co-investments.

¹ <https://www.jpiaamr.eu/>

² One Health refers to a multi-sectoral and comprehensive approach to designing and implementing programmes, policies, legislation and research to obtain optimal health for humans, animals and the environment at local, national and global levels.

In the SRIA, future joint objectives have been identified that may be implemented through co-operative activities that realign or link national investments in both research and innovation.

Six priority topics: objectives, activities and synergy

The SRA identified six research priority topics that covered the broad scope of the societal challenge posed by AMR, considering the scientific, clinical, and societal aspects of the subject. The set of prioritised research and innovation topics have been retained and updated in the SRIA forming a comprehensive One Health framework that will provide new therapies and diagnostics and prevent or minimise the emergence and spread of AMR. The SRIA defines research and innovation objectives for the six priority topics (Table 1). The majority of objectives focus purely on research, while other objectives have a clear innovation component. Innovation aspects will be addressed through strategic partnerships both with international initiatives and within the national innovation systems.

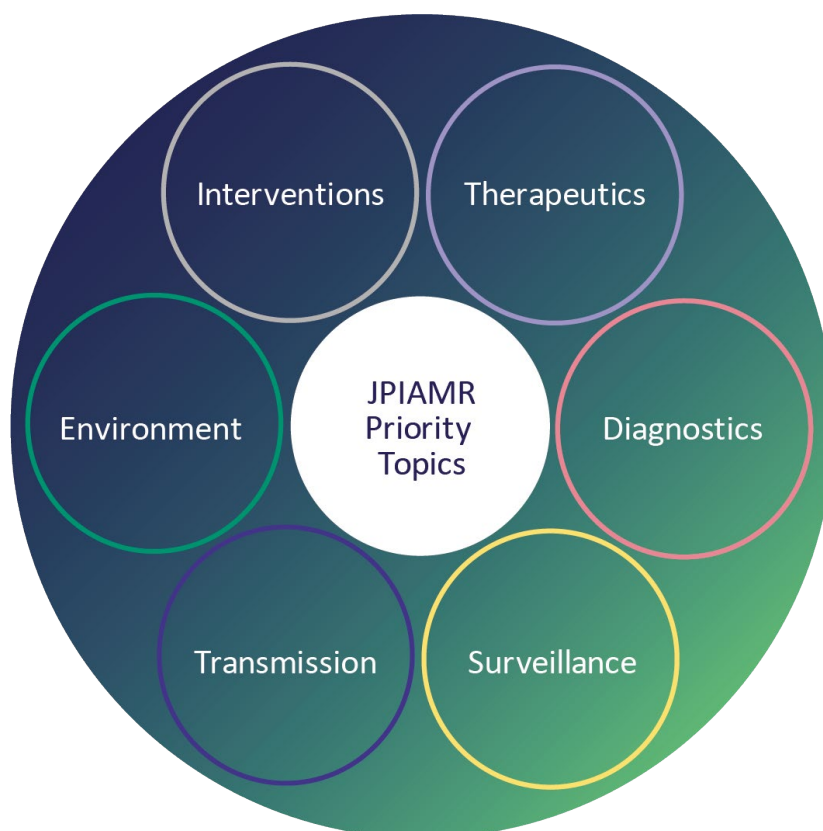


Figure 1. The six priority topics of the JPIAMR SRIA: Therapeutics, Diagnostics, Surveillance, Transmission, Environment and Interventions.

Table 1. JPIAMR SRIA priority topics and research and innovation objectives.

Priority topic	Research and innovation objectives
Therapeutics	
<i>Discovery of new antimicrobials and therapeutic alternatives, and the improvement of current antimicrobials and treatment regimens</i>	• Find new antimicrobials and targets • Develop new chemical entities and scaffolds • Improve pharmacokinetics and pharmacodynamics of antimicrobials, including neglected antimicrobials • Use personalised medicine and artificial intelligence to improve therapies • Develop alternatives for antimicrobials • Develop treatment protocols based on combination therapy using new and existing antimicrobials • Develop policy measures and economic stimuli to minimise barriers for the development, availability and introduction of new therapies and alternatives • Assess how regulation modifies and influences production and use of antimicrobials
Diagnostics	
<i>Development and improvement of diagnostics to improve the use of antimicrobials and alternatives to antimicrobials</i>	• Improve the efficacy of new and existing diagnostic tools to more effectively distinguish between infections, and/or detect antimicrobial susceptibility • Create support for the implementation of innovative technologies and linkage to data platforms promoting the use of narrow-spectrum antimicrobials • Improve the use of rapid diagnostics in appropriate One Health settings • Improve understanding and explore ways to overcome behavioural and socio-economic barriers limiting the adoption and use of rapid diagnostics
Surveillance	
<i>Optimisation of surveillance systems to understand the drivers and burden of antimicrobial resistance in a One Health perspective</i>	• Improve and standardise AMR surveillance systems, from sampling to data analysis including sampling frame, tools, methodology and reporting • Strengthen the use of surveillance data to identify human and non-human reservoirs of AMR • Optimise the use of surveillance data to estimate burden and to assess the impact of interventions • Develop novel techniques to supplement and promote the exchange of surveillance data • Improve and standardise the surveillance of antimicrobial use • Centralising registration of treatment and patient outcome

Priority topic

Research and innovation objectives

Transmission

Understanding and preventing the transmission of antimicrobial resistance

- Unravel the complex dynamics of selection and transmission of antimicrobial resistance
- Identify factors responsible for the persistence and spread of resistant organisms and resistance elements
- Determine the impact on AMR of different systems of healthcare, animal production, global trade and environmental pollution and contamination

Environment

The role of the environment in the persistence, selection and spread of antimicrobial resistance

- Determine and model the contribution of contamination sources, environmental reservoirs and exposure routes on the emergence and spread of AMR
- Evaluate the relationship between AMR and the environment, climate change, and pollution
- Assess the potential impact of industrial systems on AMR in the environment
- Develop innovative technological, policy, social, economic and regulatory approaches to mitigate AMR in the environment

Interventions

Investigation and improvement of infection prevention and control measures in One Health settings

- Develop innovative interventions aimed to detect, prevent and control the spread of AMR in a One Health perspective
- Investigate the effectiveness of AMR prevention and control strategies to increase uptake and acceptance in One Health settings
- Assess the effectiveness and cost-effectiveness of specific AMR prevention and control practices, considering different geographic and socio-economic settings
- Optimise implementation strategies, including drivers for and barriers to behavioural change, to reduce AMR
- Understand the prescription behaviours contributing to the responsible and prudent use of antimicrobials
- Assess educational and training programmes to enhance antimicrobial awareness and stewardship

Introduction

The AMR Challenge

AMR is a global health challenge that threatens advances in modern medicine. In the past 90 years since their discovery, antimicrobials have saved millions of lives from once-deadly diseases. Many treatments in modern medicine, such as organ transplant or cancer treatment, would be impossible without the use of antimicrobials to prevent infections that can occur due to immunosuppression. Antibiotics have saved the lives of millions of women who would once have died in childbirth and paved the way for treatments that were previously impossible due to the high risk of patients succumbing to post-operative infections. Invasive fungal infections are life threatening and are of increasing importance due to the expanding population of immunosuppressed patients and the limited number of available antifungal treatments.

In the last years, AMR has been recognised as a critical issue. In 2015, the World Health Organization (WHO) announced AMR as one of the greatest threats to public health. A Global Action Plan to combat AMR³ was endorsed that underscores the One Health approach involving coordination among numerous sectors and actors, including human and veterinary medicine, agriculture, environment, and finance. Since then, AMR has risen to the top of the global health agenda with various institutions weighing in, including the UN Environment Assembly, the Council of the European Union⁴, the G7⁵, the G20⁶, the European Union⁷ and the UN General Assembly⁸, that lead to the setup of the UN Interagency Coordination Group on Antimicrobial Resistance (IACG)⁹.

Several reports have attempted to investigate the impact of AMR by examining, for example, the effect on health and the cost of AMR to society. The O'Neill report estimated that more than 700,000 people per year die from drug resistant infections, and that without adequate international cooperation and intervention, this figure could rise to 10 million people by the year 2050. The report highlighted that the economic impact of drug resistance could be as high as a 3.8% loss of global gross domestic product, with global increases in healthcare costs reaching more than one trillion US dollars, and livestock output dropping by 7.5% per year. Cassini *et al.* used data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) to predict that an estimated 33,100 deaths would be attributed to infections with antibiotic-resistant bacteria in Europe alone, and that three out of four deaths could be averted by spending just two USD per person a year on measures as simple as handwashing and more prudent prescription of antibiotics. In this report, it was estimated that the burden of infections with antibiotic-resistant bacteria in the EU/EEA is comparable to that of

³ <https://www.who.int/antimicrobial-resistance/global-action-plan/en/>

⁴ <https://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-antimicrobial-resistance/>

⁵ http://www.g7italy.it/sites/default/files/documents/FINAL_G7_Health_Communique_Milan_2017_0.pdf

⁶ https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/G/G20-Gesundheitsministertreffen/G20_Health_Ministers_Declaration_engl.pdf

⁷ https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf

⁸ https://www.un.org/pqa/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf

⁹ <https://www.who.int/antimicrobial-resistance/interagency-coordination-group/en/>

influenza, tuberculosis and HIV/AIDS combined. The World Bank and the Organisation for Economic Cooperation and Development (OECD) have issued reports suggesting that from 2015 to 2050 the costs of AMR will be 3.5 billion USD per year for the expenditure in healthcare alone. In June 2017, OECD published estimates and calculations for the effectiveness and the cost-effectiveness of policies to promote effective use of antimicrobials and to prevent the spread of infections. For instance, the improvement of hand hygiene strategies could reduce the number of hospital days by 2.45 million and number of deaths by 43%, with an estimated total saving of 2.97 billion euro per year. Fungal diseases impose a considerable economic burden on healthcare systems. A report by Benedict *et al.*¹⁰ estimated that antifungal costs in the US are 7.2 billion USD per annum; however, this figure is likely underestimated. Comprehensive global estimates of the public health impact of fungal diseases are needed to improve their recognition, prevention, diagnosis, and treatment.

What is AMR?

Antimicrobials are defined as all compounds that inhibit the growth of microorganisms, and can be divided into groups based on the organisms that they target. Antibacterials, commonly known as antibiotics, act on bacteria, and antifungals act on fungi, including moulds and yeasts. Other antimicrobials include antivirals and antiparasitics. The number of infections reported with drug-resistant fungi is far fewer compared to those caused by antibiotic resistant bacteria, partly due to limited diagnostic confirmation. However, antifungal resistance is emerging as a major clinical problem. Antibiotic and antifungal resistance is perceived as a major threat to public health and is the current focus of JPIAMR activity. Throughout this document, the term antimicrobial resistance will refer to antibiotic and antifungal resistance unless otherwise specified.

Bacterial or fungal drug resistance is the ability to survive and grow in the presence of antimicrobials. Resistance is generated through gene mutation, by the acquisition of genetic information through horizontal gene transfer or by altered regulation of gene expression. Antimicrobial resistance becomes a problem when antimicrobials used to treat disease are no longer effective. The presence of an antimicrobial provides the resistant bacteria and fungi with a selective growth advantage in the infected host or environment. These resistant bacteria and fungi can then spread more widely within a population, or to other populations or environments. Environmentally driven antifungal resistance is particularly concerning since spore forming fungi do not need a host to survive or to migrate. It is critically important to understand further the emergence and spread of AMR to find ways to prevent and control infections.

AMR is particularly problematic because the discovery and development of novel antibiotics and antifungals has slowed while antimicrobial use to treat bacterial and fungal infections has increased. In addition, the routine use of antimicrobials in food animal production and in crop treatment also significantly increases the probability of developing resistance. The global challenge to address AMR goes beyond the production of new antimicrobials and therapies. Reducing demand for new antimicrobials through public awareness, infection prevention and control, and prudent, rational use of

¹⁰ Benedict *et al.* *Clin Infect Dis* 2018; 68:1791-1797

antimicrobials within a One Health approach, and the diagnosis and surveillance of antimicrobial resistant infections and antimicrobial use, are also vital in order to deal with this problem globally.

Implications for One Health

AMR is tightly linked with the One Health concept. One Health is a term used to describe a principle that recognises that human and animal health are inextricably linked, and that diseases are transmitted from humans to animals and *vice versa*. One Health also encompasses the environment as another link between humans and animals and a potential source and reservoir of AMR. Cooperation and multidisciplinary collaboration of different research disciplines and groups within society is needed to reduce and reverse the threat of AMR. To ensure a global coordinated approach to tackling the threat of AMR in the food chain, three UN agencies, the Food and Agriculture Organisation of the UN (FAO), WHO, and the UN Environment Programme have collaborated with the World Organisation for Animal Health (OIE)¹¹.

The direct threat of AMR to human health mainly occurs among the most vulnerable patients (the young, the sick, the elderly, and citizens in resource-poor settings). However, research suggests that everyone carries commensal microorganisms that have acquired resistance genes. Clearly, antibiotic resistant microorganisms have become so widespread that these organisms have become a common inhabitant of the human body and can easily spread between individuals. 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 of the microbiota is disturbed. 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 individuals for whom AMR causes the biggest burden in terms of human mortality and morbidity.

Antibiotics and antifungals are used in large quantities in modern farming practices as growth promoters, for infection prevention measures, therapeutically, or in crop treatments. Similarly, to the situation in humans, this use encourages the selection of resistant organisms, which can then spread to humans through food consumption, inhalation, contamination of the environment via animal manure, composted cropping materials, dust or insects that populate farms, and through direct contact of humans with animals. Nevertheless, relying on antibiotics to sustain animal production is unjustifiable and measures need to be taken to minimise the misuse of antibiotics in animal husbandry. Similar measures need to be taken to ensure appropriate use of antifungals in crop treatments and prevent the emergence of clinical antifungal resistance. Besides being a potential threat to human health, AMR also complicates the treatment of infections in animals, which negatively influences animal welfare and may threaten food production.

¹¹ http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/tripartite/en/

The EU-wide ban on the use of antibiotics as growth promoters came into effect in 2006. In 2018, a revised regulation on veterinary medicinal products proposed limiting the use of antibiotics in prophylaxis and metaphylaxis. However, the total amount of antibiotics used in veterinary medicine – both preventative and curative – is still too high in most EU countries. Antibiotics are mostly administered orally (for example by mixing through 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 and jeopardising the protection from pathogenic organisms afforded by commensal bacteria. Several European countries have initiated programmes to reduce, and even restrict, the use of antibiotics in veterinary medicine. Research on such programmes indicates that a massive reduction in antibiotic use can be achieved with minimal cost to animal welfare and the profitability of farms. This also provides an opportunity for natural experiments to investigate whether the use of antibiotics in animals drives AMR.

The extent to which food production (of either animal or plant origin) contributes to the burden of antimicrobial resistant infections is a subject of considerable debate. However, it is important to note that much of the food that is consumed in Europe, or other countries with strict antimicrobial regulations, is produced in parts of the world where antimicrobial usage may be less well-regulated, and therefore may be substantially contaminated by either antibiotic or antifungal residues or antimicrobial resistant microorganisms. The FAO, the WHO and the OIE collectively drew up a list of critically important antimicrobials¹² in both human and veterinary medicine. This list is updated regularly. Since many antibiotics are used in both humans and animals, a careful balance needs to be struck between using antibiotics for animal health while preserving the efficacy of critical antibiotics for human use. A similar balance needs to be obtained for antifungals used in agriculture and human medicine.

Implications for the UN Sustainable Development Goals

In resource-poor settings, as a result of poor water quality, hygiene and sanitation limitations, climate conditions and inadequate healthcare systems, the problem of AMR is even more dire and threatens the capacity to achieve several of the UN Sustainable Development Goals (SDG)¹³. The high prevalence of infectious disease, poor access to healthcare facilities, and unregulated antimicrobial use aggravates the situation further. In many countries, the problem is the lack of access to antimicrobials, rather than their misuse. Rising population, increasing global trade and travel will further escalate the situation.

¹² <http://www.fao.org/3/a-i0204e.pdf> Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials Report of the FAO/WHO/OIE Expert Meeting. Rome 26-30 November 2007

¹³ <https://www.un.org/sustainabledevelopment/sustainable-development-goals/>

The background is a vibrant blue with a complex, layered design. It features several overlapping circles of varying shades of blue. A network diagram with interconnected nodes and lines is visible, particularly in the upper left and lower right. There are also circular patterns resembling gears or orbits in the lower right. The overall aesthetic is modern and technological.

Priority Topics

Therapeutics

Discovery of new antimicrobials and therapeutic alternatives, and the improvement of current antimicrobials and treatment regimens

The focus of this priority topic is to improve current antimicrobial treatment by enhancing discovery of novel antimicrobials, treatment strategies and alternative therapeutics, as well as by optimising drug use, dose and delivery. An additional aim is to initiate research into the possibilities and effects of minimising barriers for the introduction of novel antimicrobials and anti-infective compounds by simplification of regulatory procedures and by stimulating economic incentives.

Introduction

The technical challenge of developing new and innovative antimicrobials is a major factor contributing to the general decline in the production by pharmaceutical companies. Combined with the difficulty to recuperate costs for drug discovery of antimicrobials, which are challenged by resistance within a decade or so, the number of antibiotics and antifungals in the development pipeline has decreased to critical levels. The availability and development of antimicrobials for use in the paediatric population is even more limited, and appropriate studies need to be conducted to ensure availability of therapeutic treatments for this demographic. Eight new antibiotics (including one for the treatment of TB) have been approved since 2017, however only two were classified as innovative and none were directed towards the WHO priority pathogens *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. In 2019, the WHO conducted a review of publicly available information on the current clinical development pipeline of antibacterial agents to assess the extent to which the drug candidates act against the WHO priority pathogens. The report, that was limited to new therapeutic entities (NTEs) in phase 1-3 clinical trials, revealed that a total of 50 antibiotics (including combinations) and 10 biologicals were in the clinical pipeline, with 32 new therapeutic entities (33 antibiotics and 11 biologicals) that target priority bacterial pathogens. Among the 32 antibiotics that are under development for priority bacterial pathogens, only six are considered innovative¹⁴.

Fungi are eukaryotes with a relatively high degree of phylogenetic similarity to humans and therefore they offer relatively few (3-4) differential targets that can be exploited for antifungal drug development. A refreshed and sustainable pipeline of antifungal agents is urgently needed.

Although academic laboratories continue their research efforts to identify new drug leads, collaboration with pharmaceutical companies to conduct broader pre-clinical research and to translate the results to the market is needed¹⁵. Since 2008, the

¹⁴ <https://apps.who.int/iris/bitstream/handle/10665/330420/9789240000193-eng.pdf>

¹⁵ <https://www.fda.gov/Drugs/InformationOnDrugs/>

Innovative Medicines Initiative (IMI) has been fostering public-private partnerships (PPPs) to drive transformational advances in the way drug discovery and development of new antibiotic agents is performed. IMI now focuses on target validation and biomarker development, adoption of innovative clinical trials paradigms, innovative medicines, and patient-tailored adherence programmes. Funding initiatives, such as CARB-X¹⁶, Novo-REPAIR¹⁷, EU InnovFin¹⁸ and GARDP¹⁹ (a not-for-profit drug development organisation) also have a strong focus on the development of new antibacterial therapeutics. Other EU initiatives, such as the Orphan Drug Regulations and the EMA's PRIME scheme, encourage, support and expedite the progression of potential therapeutics through the drug development lifecycle. For antifungals, the situation regarding the development of new antimicrobials is even direr, with few, if any, private partner organisations committing support to development of new therapeutics. The Drugs for Neglected Diseases *initiative* (DNDi) is involved in developing effective and affordable treatment for fungal diseases²⁰ and an IMI project focuses on affordable green manufacturing of antimicrobials, including antifungals²¹.

Currently, leading organisations and governments across the world have either developed, or are developing, coordinated action plans to effectively control and manage the risk associated with AMR. The Global Action Plan to combat AMR introduces five strategic objectives and one of them focuses on research and innovation to strengthen actions on research and development (R&D) of new antimicrobials and alternatives. In the 2017-2019 work plan of the IACG²², the supplemental objectives included ensuring sustainable production and access to existing and future antibiotics and other antimicrobial medicines, and the need for new R&D models for medicines, vaccines, and diagnostics, based on the delinkage principle²³ with the identification of models for private sector engagement. In fact, effectively targeting drug resistance requires a complex multitiered strategy in which the development of antimicrobial agents with novel mechanisms of action, and new therapeutic alternatives, play a crucial role. It should be noted, however, that in all steps of research the sharing of negative findings is important to be able to achieve results.

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

¹⁶ *Combating Antibiotic Resistant Bacteria*

¹⁷ *Novo Holdings established REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund.* <https://www.repair-impact-fund.com>

¹⁸ *EU Finance for Innovators*

¹⁹ *Global Antibiotic Research and Development Partnership*

²⁰ <https://dndi.org/research-development/portfolio/fosravuconazole/>

²¹ <https://www.imi.europa.eu/projects-results/project-factsheets/chem21>

²² <http://www.who.int/antimicrobial-resistance/interagency-coordination-group/en/>

²³ *De-linkage principle refers to innovative mechanisms to ensure access - without limiting incentives - to develop and make new drugs available.*

Ideally, drugs already used in the animal and agricultural sectors should not be used or further developed for use in humans.

Challenges

Fundamental, translational and clinical research must provide innovative solutions to address infection prevention, diagnosis and treatment. This research should also provide avenues for new therapies and information for the optimal use of new and existing drugs, including maximising the availability for the paediatric population. IMI is important in moving candidate antimicrobials, that are currently in the development pipeline of pharmaceutical companies, to clinical trials and, eventually, into clinical practice. However, preclinical research into understanding how bacteria and fungi resist the actions of antimicrobials, and identification and exploitation of additional targets for antimicrobial therapy, are also fundamental for ensuring that the drug pipeline is continually replenished. Replenishing the drug pipeline with candidate lead compounds with clinical potential is needed, as new and existing antimicrobials will continue to become obsolete due to the selection for, and transmission of, resistance.

Research into antimicrobial therapeutics should include the development of novel drugs that aim to affect the infection cycle, not solely on the potential to kill or reduce the growth of bacteria and fungi. Studies of alternative strategies, such as those that target virulence mechanisms should also be pursued, 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, including vaccination, immunomodulation and innovative delivery solutions. Therapeutic use should be linked to personalised medicine, where accurate and rapid diagnostic tests directly connect with effective therapy. Systems biology can shed light on mechanisms of action, identify targets for rational clinically useful combination chemotherapy to suppress or minimise resistance, drive drug repurposing, and provide a framework for the discovery and development of novel antimicrobial interventions and therapeutics. Research into innovative combinations of compounds (multiple antimicrobials used simultaneously, or antimicrobials combined with other anti-infective agents) also hold great promise, as does the development of compounds that may inhibit the emergence and transfer of antimicrobial resistance.

The JPIAMR recognises that the challenges faced by big pharma are different to those of small and medium enterprises (SMEs). What is considered “pre-competitive” for big pharma is “competitive” for SMEs because innovation is a value chain in which SMEs are at the beginning and big pharma at the end. Streamlining the clinical trial evaluation and regulatory assessment pathways is an important aspect of the translation of research outcomes. The sharing of negative data also has different consequences; for big pharma negative data about a line of enquiry can decrease economic performance for the company overall, while for SMEs this could be perceived as a “negative signal” and jeopardise the future of the company. The JPIAMR recognises the need to support collaboration between academics and industry through funding networks to determine best practice, develop a framework for research and governance structures for research funded with industry partners, and through advocacy to streamline the process involved with obtaining positive research outcomes translated into products, services and policy.

Opportunities must be created to translate fundamental discoveries in microbiology into antimicrobial drug discovery programmes, engage with industry to overcome barriers towards engagement with academia, and create models to improve the international coordination of regulatory processes (i.e. effective drug registration, regulatory processes and pricing strategies). Finally, considering the abundance of bacterial and fungal infections that pose a health threat in resource-poor settings, it should be ensured that effective and affordable therapeutics, and structures to support their appropriate use including diagnostics and laboratory infrastructure, are globally accessible.

Research and innovation objectives and activities

Find new antimicrobials and targets

Finding new antimicrobials and targets is an essential strategy to overcome resistance. Discovery of novel antimicrobial classes, active against new targets and with acceptable pharmacokinetic and safety profiles, is complex. Research on early stages of antimicrobial discovery and development (i.e. prior to the clinical trial phase) are critical to deliver new and innovative antibiotics and antifungals based on traditional and novel technologies, including nanotechnologies. Additionally, clinical trials evaluating efficacy are difficult and expensive; they can be complicated by the absence of rapid diagnostic tests to facilitate patient recruitment, limited incidence of disease and by the need for combination therapy and prolonged patient follow-up. Antifungal clinical trials have the added difficulty in enrolling complex patients who have a multitude of clinical problems. New approaches to streamline and de-risk both preclinical development and early phase clinical studies could maximise the probability of a new drug ultimately succeeding in the clinic and shorten the time for this to occur. The application of “omics” technologies (e.g. genomics, metabolomics, proteomics, and transcriptomics) in combination with powerful bioinformatic tools would enable modelling of key signalling pathways in the host-pathogen interplay and could be useful to find new antimicrobial targets. Moreover, in order to identify new antimicrobial targets, research is needed to generate insights into the mechanisms of resistance, gene transfer, and adaptive microbial evolution (fitness and virulence), including the action and role of persistence, host-pathogen interactions and antimicrobial resistance reversal. Efflux pump systems should be considered in strategies for finding new targets, since they are involved in expelling drugs from bacterial and fungal cells.

Develop new chemical entities and scaffolds

Innovative synthetic biology or chemistry strategies to develop novel chemical scaffolds for antimicrobials active on validated targets but capable of overcoming resistance mechanisms are needed. For antibiotics this could include, for instance, identifying agents that inhibit peptidoglycan cross-linking and that are structurally unrelated to beta-lactams, which act on the same target but with different modes of action or new interaction sites, or the development of nanoparticles and nanostructures for targeted drug delivery. New methodologies that identify physicochemical properties of antimicrobials must be encouraged, as well as approaches affecting the ability of small molecules to enter Gram-negative bacteria, such as the work done within the

TRANSLOCATE project²⁴. Novel chemical scaffolds require appropriate characterisation of physicochemical properties, but this is a time-consuming process. The rapid characterisation of new resistance mechanisms is also critical to this purpose. Other difficulties in finding compound candidates include solubility of compounds, stability, toxicity, specificity, drug penetration to the site of infection, route of delivery and efficiency. Discovery of new antimicrobials should concentrate on “green chemistry” and biodegradable scaffolds, and enzybiotics, to minimise the environmental impact of antimicrobial production and use. Potential environmental selection of AMR in agricultural wastes such as compost, water or other environmental compartments triggered by drugs residues may favour AMR spread.

Improve pharmacokinetics and pharmacodynamics of antimicrobials, including neglected antimicrobials

Resuscitating neglected antimicrobials by improving pharmacokinetics and pharmacodynamics (PK-PD), reducing side effects and modifying dosage/delivery issues (e.g. providing incentives for the development of oral formulations for community infections and outpatient treatment) would enable the use and reuse of already discovered drugs to treat infections. Appropriate routes of administration should focus on maximising delivery of the drug at the site of infection. Appropriate PK-PD research and clinical trials are needed on combinations of (old and new) drugs, and on the development of pathogen-specific combinations. PK-PD varies among patients and is related to demographic group and pathophysiological profile, resulting in adverse reactions due to toxicity, as well as suboptimal drug concentrations at the infection site that impact the outcome and the development of drug resistance. In the light of the personalised medicine approach tailoring antimicrobial selection and dosing to specific patient categories, the PK-PD investigations should also be extended to patient groups not covered in registration trials (e.g. obesity, burns, neonates, paediatrics, cystic fibrosis, transplant, extracorporeal circuits, and malnutrition).

Use personalised medicine and artificial intelligence to improve therapies

Addressing research on personalised medicine and the careful targeting of antimicrobials could optimise their safety and clinical and cost effectiveness. Rapid diagnostics are essential for optimal antimicrobial selection. Whole-genome sequencing technologies have improved the understanding of resistance and allowed a rapid identification of resistance mechanisms in multiple organisms. Whilst recognising that presence of a resistance gene does not always equate with clinically relevant drug resistance, the introduction of resistance mutation databases would aid patient management, enabling personalised treatment. There is an urgent need for personalised management through drug resistance screening in certain patient groups. Clinical trials addressing implementation of personalised therapies according to geographical and care appropriate settings, local epidemiology, age, gender, metabolism and clinical characteristics are needed. Furthermore, it is essential to address social and behavioural factors that contribute to personalised medicine. Findings should be translated into implementation strategies for use in clinical medicine.

²⁴ <https://www.imi.europa.eu/projects-results/project-factsheets/translocation>

Innovative tools applying artificial intelligence (machine-learning application for risk definition, decision support systems for personalised therapies) need to be explored and connected with rapid diagnostics.

Develop alternatives for antimicrobials

Alternatives to antimicrobials, which could be useful to complement the activity of antimicrobials, should be used to overcome and reduce resistance selection and adverse effects associated with antibiotic and antifungal use. Specific alternatives could address all parts of the infection life cycle, for example anti-virulence strategies, bacteriophages and fungal viruses, enzyme blockers, nanomedical solutions, molecular scissors, antimicrobial peptides, anti-biofilm agents, prevention of sporulation (fungi) or host defence peptides. Specific vaccines need to be developed for the prevention of infections and to prevent the development of multi-drug resistant (MDR) strains. R&D opportunities have been reviewed in a report from the Wellcome Trust²⁵. When developing new antibiotics and antifungals for veterinary medicine and agricultural sectors, capabilities of cross-resistance to antimicrobials for human medical use should be carefully evaluated. A guidance for such evaluation needs to be developed which include wildlife bacterial and fungal diseases and a comprehensive One Health approach.

Develop treatment protocols based on combination therapy using new and existing antimicrobials

The role of novel and innovative combinations of compounds (antimicrobials, and combination therapy using new/existing antimicrobials and non-antimicrobials) should be investigated in mitigating the development of antimicrobial resistance in fungal and bacterial pathogens, as well as in situations of co-infections. Research on combination treatments would best address differences in pharmacology of the combined agents as well as potential adverse interactions, impact on microbiota, and cost effectiveness of the therapy. Persistence is a less studied area and the role of combination treatments to eradicate persistent organisms should be investigated in those infections that are clinically relevant and with a validated treatment outcome. Combination antimicrobial therapy to prevent the emergence of resistance (and enhance efficacy) is a proven strategy for an increasing number of bacterial and viral infections (for example, tuberculosis, HIV, Hepatitis C), and is standard practice for the treatment of fungal (cryptococcal) meningitis. Nevertheless, combination therapy to prevent resistance is still very much underused and under-researched for treatment of bacterial and fungal infections. The pharmaceutical industry does not often prioritise developing combination therapies, leaving this space to less well-funded academia. There is a need for a coordinated approach to the exploration and development of combination treatments of old and new antimicrobials - from early stage screening for development of combinations, including screening for new compounds in the context of partner compounds, through to pre-clinical investigation of combinations in careful PK/PD animal models, and clinical trials.

²⁵ Wellcome Trust and The Boston Consultation Group. *Vaccines to tackle drug resistant infections. An evaluation of R&D opportunities*. London: Wellcome Trust, 2018 (<https://vaccinesforamr.org/>)

Develop policy measures and economic stimuli to minimise barriers for the development, availability and introduction of new therapies and alternatives

The decreased interest of pharmaceutical companies in the development of antimicrobials could potentially be overcome by improving policy measures and new economic stimuli to minimise the barriers in antimicrobial R&D. Similarly, regulatory enablers for the use of combination therapies shown to prevent resistance are needed. The necessity of innovative economic models for drug discovery, different to “free market economics”, must change across clinical phases connected with harmonising regulatory processes and developing new pricing strategies, for example delinking price with the volume of sales. Overlapping and synergistic approaches need to be coordinated at national and international levels. Further economic research needs to clarify the drivers of AMR in low and middle-income countries (LMICs), engaging local stakeholders to ensure widespread access, distribution and implementation. A multifaceted approach involving SMEs to improve the efficiency of research, and lower costs, should be encouraged. This should be carried out in alignment with research programmes, such as IMI²⁶ New Drugs for Bad Bugs (ND4BB), the Biotech companies in Europe combating Antimicrobial Resistance Alliance (BEAM)²⁷, the European Gram-negative Antibacterial Engine (ENABLE) project²⁸ (with the participation of European Federation of Pharmaceutical Industries and Associations (EFPIA), research bodies, SMEs and third parties), and the Driving Reinvestment in Research and Development and responsible antibiotic use (DRIVE-AB)²⁹ project that proposed push and pull incentives to policy makers. In addition, large-scale research and development initiatives for antifungals need to be put in place.

Assess how regulation modifies and influences production and use of antimicrobials

Policy regulation can modify and influence antimicrobial production and usage. For this reason, country and research policies need to take a One Health approach across agriculture/food production, environment and healthcare. Acquisition, persistence, and transmission of AMR by humans, animals, agriculture and the environment is affected by many factors, including limited clean water, the implementation of infection prevention and control measures, provision of drugs and diagnostics, farming systems with suboptimal regulation of antimicrobials, biosecurity and hygiene, and population densities. Assessment of the effects of these factors is required. In many countries, antimicrobials are freely available without prescription, with access in pharmacies etc., impeding the measurement of the quantity of antimicrobials consumed. National regulations are needed to improve the control of drug quality, marketing/sales and use particularly considering generics production, in LMICs and the unlicensed internet sales of antimicrobials that facilitate the use of poor-quality drugs (falsified, substandard, or degraded).

²⁶ <http://www.imi.europa.eu/projects-results/project-factsheets/nd4bb>

²⁷ <https://beam-alliance.eu/>

²⁸ <http://nd4bb-enable.eu/>

²⁹ <http://drive-ab.eu/>

Diagnostics

Development and improvement of diagnostics to support the use of antimicrobials and alternatives to antimicrobials

The goal of this priority topic is to stimulate the design, development, evaluation and implementation of diagnostic tests for the treatment and prevention of infections, particularly those caused by antimicrobial-resistant organisms. The use of diagnostics and detection of drug susceptibility will support rational clinical decision algorithms leading to a targeted, more sustainable use of antimicrobials and improved tracking of AMR.

Introduction

A radical change in the way antibiotics and antifungals are used is necessary since it is estimated that 70% of antibiotics and 75% of antifungals (in invasive infections) are prescribed and used incorrectly, i.e. in the absence of a bacterial or fungal infection or for infections resistant to the antimicrobial treatment. This incorrect use largely results from physicians and other users of antimicrobials being unable to make a precise diagnosis of infections in real-time. Unless diagnostics for bacterial infections and the detection of susceptibility are improved, physicians and veterinarians will continue to prescribe antibiotics in any case in which they suspect that the patient or animal may have a bacterial infection requiring treatment. Diagnosis of fungal infection is even more problematic with few, if any, diagnostics available to aid the timely prescription of antifungals and appropriate use in the clinical and agricultural settings.

As the overall volume of antibacterial and antifungal use is associated with drug resistance, the development and use of rapid and cost-effective diagnostics to detect bacterial and fungal infections and antimicrobial susceptibility would reduce antimicrobial resistance. Within this context, the use of the word “diagnostic” will encompass not only differentiation between bacterial and non-bacterial, and fungal and non-fungal, infections, but also, when appropriate, microbe speciation and detection of antimicrobial susceptibility. Special attention should be directed towards the development of diagnostics that can be used for detection of infections and resistance in paediatric patients. In a more general context, surveillance of the emergence and distribution of multidrug resistance is important for understanding AMR in One Health and to guide public health measures.

The implementation of rapid diagnostics for bacterial and fungal infections and antimicrobial susceptibility also requires major behavioural changes by clinicians, veterinarians and patients who will still need to wait for the result of a rapid test before narrow-spectrum antimicrobials can be prescribed and used. The effect of the wide-scale introduction of rapid diagnostics on minimising the emergence and spread of AMR needs to be quantified and justified with respect to human and animal health, and the cost associated with diagnostic use. The success of novel diagnostics will also depend on using appropriate reimbursement mechanisms and non-financial incentives. Cultural,

contextual and behavioural determinants influence antimicrobial use and may determine which technologies and methods are most cost-effective and/or can be successfully implemented.

Cost-effective assessments and implementation research to inform decision-making are needed on a global basis in order to address the crisis of AMR. Given that AMR spreads across national borders freely, the response to AMR in resource-poor settings has global consequences.

Companion diagnostics will facilitate antimicrobial development, particularly of narrow spectrum antibiotics and antifungals, by reducing the cost of clinical trials and enabling focused enrolment of patients infected with the targeted pathogens. Ideally, (companion) diagnostics would accompany the development and approval of new antimicrobials to delay the development of resistance to these compounds and to enable their use within the scope of personalised medicine.

It is expected that the use of rapid and early diagnostics could reduce the purely preventive use of antimicrobials in veterinary medicine. For food-producing animals, the rapid and early detection of sick animals in the herd is important. Identification of infection at the individual level would allow targeted subsequent treatment of individuals or smaller groups (pen, corral). Diagnostic tools should be adapted to health monitoring and artificial intelligence should be used to implement warning signals. Technologically, the tests for veterinary applications should not differ significantly from those used in human medicine, however different sampling techniques and protocols are likely necessary to efficiently assess different pathogens in herds and stables. For this purpose, the engagement of industry is needed. The use of rapid testing in the food chain between primary production and the consumer would also rapidly identify food products contaminated with antimicrobial-resistant organisms, thereby increasing food safety. Within the One Health context, the topic of diagnostics should also involve new methods for monitoring of AMR in the environment, including in agriculture and aquaculture.

Novel technologies have already been developed to identify microbial pathogens and antimicrobial resistance elements, and if put to effective use, many of these technologies could aid antimicrobial prescription and use. Although implementation of these new technologies has the potential to improve infection outcome, they typically increase costs of care since innovators often focus more on the outcomes achieved rather than on the value delivered. This occurs particularly since many diagnostic tests have not been developed with the reality of both human health and animal care in mind, including current clinical practices, primary care and hospital infrastructure, animal management practices, and research to develop the economic case. Hence, the uptake of these novel technologies has been limited. Antibiotics are considerably less expensive to produce than antifungals. In contrast to antibiotics, the financial cost of using diagnostics for fungal infections would likely outweigh the cost of antifungal treatment itself.

It is expected that technological innovations, which allow personalised human and veterinary medicine, will increase, rather than lower costs associated with diagnostics.

Consequently, if these new technologies are to be successfully implemented in the future, new smarter and cost-effective holistic care for both human and animal populations must be developed, evaluated, and assessed with respect to the risk of increasing AMR. The current practice of inappropriately using and over-prescribing antimicrobials must be minimised with appropriate diagnostics. The successful introduction of early diagnostics in part depends on the awareness and empowerment of patients who can be provided with quality information and strategies to improve health literacy that would result in appropriate medicine taking behaviour. Health-literate patients have better health outcomes and higher quality of life, better awareness and knowledge about medicine use, and take greater responsibility for their own health. These patients are better at providing vital information and asking pertinent questions, which in the end promotes rational use of diagnostics and therapeutics. In the agricultural sector, educational efforts should be aimed at farmers who need to understand the benefits of rapid testing in terms of both sustainable use of antimicrobials and a reduction in economic losses from disease among their animals and crops. Finally, significant differences exist between the needs of the high-income countries (HIC) and LMICs, and the recognition that strategies to approach the use of diagnostics will likely differ in different cultural and socio-economic settings.

Challenges

The development of rapid diagnostics requires secure funding for periods long enough to ensure their development from concept to production. This could be done by encouraging public-private partnerships to support sustainable innovation and synergy between academic centres and industry, 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 identify real markets, where rapid (point-of-care) diagnostics in human (both adult and paediatric) and animal healthcare, agriculture, aquaculture or environmental surveillance really matter enough to purchasers to drive demand and to encourage insurance companies or governments to pay for, or subsidise, their use.

A global platform to evaluate rapid diagnostic tests by aligning payers and providers, as well as engaging those who use and benefit from these rapid tests, would be beneficial in addressing AMR. The unique collections of clinical material and strains that have been gathered during the course of many funded projects in the EU and in JPIAMR member countries, and other regions as appropriate, 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.

Research and innovation objectives and activities

Improve the efficacy of new and existing diagnostic tools to more effectively distinguish between infections, and/or detect antimicrobial susceptibility

The development of novel diagnostics must be driven by an existing need of stakeholders in healthcare (adult and paediatric), veterinary, agricultural and

environmental settings where AMR is a challenge, as well as address the implementation into resource-poor settings such as LMICs, where required. The development and use of diagnostics based on different technologies to accurately identify infections and distinguish between bacterial and non-bacterial infections, and fungal and non-fungal infections, is critical for aiding antimicrobial prescribing practices. However, diagnostics must be further expanded to identify specific pathogens and evaluate patterns of antimicrobial resistance or susceptibility, at least to commonly used human, veterinary and agricultural antimicrobials. Tests are needed to differentiate reliably between colonisation and infection, as well as to identify non-severe infections that help predict which patients are at high risk of an unfavourable outcome if untreated. Ultimately, these diagnostics would be culture-independent, affordable, rapid and ideally at point-of-care. If such diagnostics are developed, their application to surveillance and monitoring of AMR may also be possible.

For the next generation of novel diagnostics, new cost-effective platforms that integrate innovative technologies need to be developed. These novel platforms should be faster and less expensive 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.

In particular, clinical breakpoints are needed in veterinary medicine for each "bacteria - animal species - antibiotic". Clinical breakpoints are urgently needed in both human and veterinary medicine for fungal infection treatment. For fungal infections, strong epidemiological and environmental surveillance data in relation to AMR should be collected and used to guide prescribing.

Create support for the implementation of innovative technologies and linkage to data platforms promoting the use of narrow-spectrum antimicrobials

Well-designed pre-clinical studies and clinical trials, as well as farm and environmental studies, need to be conducted to evaluate the use of innovative 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, animal production, farming practices, environmental management, and surveillance systems need to be evaluated. 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, encompassing accessible biobanks and global web platforms for industry and academia should be created and enriched with data from the healthcare, agricultural, veterinary and environmental settings. This knowledge base will help to deliver new diagnostic tests and improve current assays, and should include collections of several thousand of microbial strains and purified genomic DNAs, sequences of genes, panels for quality control testing and well-characterised clinical samples with relevant clinical information. Tests should also take into account practicality and ease of use.

Improve the use of rapid diagnostics in appropriate One Health settings

Once new diagnostics have been developed, their clinical validity (in terms of improved outcomes), clinical utility (improved decision-making by physicians and veterinarians

and improved access), agricultural and environmental applicability (by detecting AMR in agricultural settings and the environment to support prevention and control measures) and cost-effectiveness need to be studied in different One Health settings where exposure can occur. Accurate identification and antifungal susceptibility testing are still major challenges, and many laboratories worldwide lack this capability. Barriers to the acceptance and uptake of rapid diagnostic tests can be identified through a combination of behavioural sciences, economics, and social science. Identification of such barriers can be beneficial in understanding behavioural factors that may help in overcoming the hurdles that limit the use of these tests in the treatment of people and animals as well as in agricultural and environmental management. Comparative studies between countries regarding the relative use of current rapid diagnostics in One Health settings will allow the identification of factors (including differences in reimbursement and incentive systems, regulatory frameworks, and economical limitations and restrictions) that hinder suitable use of rapid diagnostics in rational decision-making regarding antimicrobial usage. Mechanisms for empowering populations, healthcare professionals, farmers, and users and producers of antimicrobials affecting environmental exposure to create value-conscious consumers and patients regarding the benefits of rapid diagnostic tests in terms of better treatment and minimising antimicrobial usage need to be identified.

Improve understanding and explore ways to overcome behavioural and socio-economic barriers limiting the adoption and use of rapid diagnostics

Clinical studies understanding the behavioural barriers for the use of novel diagnostics by medical and veterinary staff are needed. Studies should also develop clinical and economic models identifying the epidemiology and associated cost of AMR (including cost to society of future resistance to antimicrobials). Such models can provide the baseline to evaluate the incremental costs and benefits of new diagnostics to healthcare systems and society. Currently, the price of diagnostics is relatively high in comparison to the cost of antibiotics, leading to the behaviour that antibiotics are overused in inappropriate circumstances. Treatment of fungal infections is comparatively expensive and therefore the availability and use of rapid diagnostics could actually have an economic benefit. Cost-effectiveness analyses through comparisons with standard approaches for the diagnosis of infectious diseases and preventing exposures to AMR should be supported by studies evaluating the appropriate use of new diagnostics and the implementation of reimbursement systems. The development of novel diagnostics needs to be supported by sustainable business models that result in innovation, long-term investment, and public private partnerships (PPPs). Interactions between PPPs will also provide a framework to plan and coordinate technology development that corresponds to current and future needs of clinicians, veterinarians, food safety experts, agricultural users of antimicrobials and environmental health science experts. In addition, those who pay for diagnostics, especially healthcare insurance companies, need to be involved. Specific public health, patient, agricultural and environmental health issues need to be identified where a point-of-care, farm or environmental management solution matters enough to purchasers to drive demand and ensure that insurance companies or governments pay a fair price.

Surveillance

Optimisation of surveillance systems to understand the drivers and burden of antimicrobial resistance in a One Health perspective

The goal of this priority topic is to strengthen the research on surveillance methods to improve and extend surveillance of AMR and on antimicrobial use in One Health settings. Optimisation of surveillance systems need to consider the existing surveillance and research networks hosted and coordinated by international partners such as the European Centre for Disease Prevention and Control (ECDC), the European Medicine Agency (EMA), the European Food Safety Authority (EFSA), World Health Organization (WHO), Advisory Group on Integrated Surveillance of AMR (AGISAR), and others.

Introduction

Surveillance is the continuous, systematic collection, analysis and interpretation of data needed for action, e.g. planning, implementation, and evaluation of prevention and intervention practices. International surveillance of AMR and antibiotic and antifungal use is essential to monitor the threat of AMR and to guide and evaluate policy measures. AMR surveillance, including the standardisation of data management, is needed for One Health policy purposes to understand the development, transmission and directionality of the spread of AMR, to estimate the burden of resistance in all global settings, and to guide policy makers in targeting crucial AMR prevention and control measures. Surveillance serves as a warning system and strengthens the response to the occurrence and outbreak of antimicrobial resistant organisms by signalling the emergence and initial spread of resistance genes and bacteria and fungi in human and animal health, food production and the environment.

In May 2015, the World Health Assembly approved a Global Action Plan to combat antimicrobial resistance. One of the five strategic objectives of the action plan was to strengthen the evidence base through enhanced global surveillance and research. The WHO has developed the action plan in close collaboration with FAO and OIE to coordinate across sectors and to improve current national and international surveillance.

A global AMR surveillance network – covering all countries – would encourage a united front against the threat of AMR. In addition, global monitoring of antibiotic and antifungal use would encourage participating countries to adopt regulations to control the use of antimicrobials in human and animal health, food production and agricultural sectors. The One Health approach in surveillance and infection prevention and control ensures that all sectors are engaged.

Launched in October 2015, the Global Antimicrobial Resistance Surveillance System (GLASS)³⁰ promotes and supports a standardised approach to the collection, analysis and sharing of AMR data at a global level by encouraging and facilitating the establishment of national AMR surveillance systems. GLASS initially focused on surveillance data on human priority bacterial pathogens considered to be the greatest threat globally, and progressively incorporates information from other surveillance systems related to AMR in humans, such as foodborne AMR, monitoring of antimicrobial use and surveillance of healthcare associated infections (HAI). By the end of the first data call on 8 July 2017, GLASS collected aggregated national level data from 42 countries. Over time, the system will enable comparable and validated data on AMR to be collected, analysed and shared between countries and partners. Capacity building and early implementation guidelines are provided in the GLASS manual and through technical country visits. National and international systems for surveillance of fungal pathogens need to be implemented. The WHO is currently developing a list of priority fungal pathogens that could be used as a basis for an antifungal surveillance system.

Challenges

The current existing international and national surveillance systems do not meet all the needs and expectations of policymakers, public health workers and researchers. There is a large heterogeneity across countries in the levels of surveillance systems with respect to:

- quality and nature of data collections;
- data source and sampling frame;
- state-of-the-art microbiological diagnostics and the ability for early detection;
- quality of antimicrobial susceptibility testing; and
- availability and quality of national reporting systems.

Furthermore, these surveillance systems do not cover all components of One Health - most are directed at human and veterinary health. Moreover, most systems include culture data, and only a few surveillance systems contain molecular and genotyping analyses or details on patient outcome. Overall, the absence of a common surveillance reporting system hampers the integration of data from different surveillance systems across sectors and countries. Standardisation of certain components (e.g. targets, metadata, and detection and typing methods) across surveillance systems would improve the exchange and comparison of data across sectors and countries. The minimal information on samples required for their use in R&D and surveillance needs to be defined.

The use (and misuse) of antimicrobials is the most important driver for the emergence, selection and spread of AMR. Therefore, it is of utmost importance to collect data on AMR and on the antibiotic and antifungal use that will lead to a better (integrated) understanding of the burden and drivers of AMR in different One Health settings. This is particularly critical for antifungals, where surveillance data on antifungal use and resistance is scattered and limited. The methods, study design and sampling frame strategies for surveillance of the use of antibiotics and antifungals in food production

³⁰ <http://www.who.int/glass/en/>

and agriculture needs to be strengthened. Data can be used for benchmarking, which is a useful tool to inform and influence users, prescribers and hospitals to improve their practices.

Globalisation, manifested by the increase in tourism, international trade of foods and goods, and changing migration patterns, will contribute to the rapid spread of AMR around the world. Therefore, travel, migration, demographics and trade logistic data need to be integrated into AMR surveillance systems to better understand the attributable proportion of these factors to new and existing resistance patterns in One Health. Infrastructure and land use data can enlighten the level of sanitation and manure/compost application influencing the environment.³¹

Current surveillance systems, listed in the table below, could be used as blueprints, which could be extended in terms of international coverage, scope of genetic data and patient outcome. In Europe, the expansion of EARS-Net³² to Central-Asia and Eastern Europe has been launched and implemented by the WHO Regional Office for Europe in the Central Asian and Eastern European Surveillance of Antimicrobial Resistance ((CAESAR) network³³. Extending surveillance to transient human populations (migrants, travellers), environmental sources, hotspots and key reservoirs is also needed and should be integrated and harmonised with surveillance in healthcare and farming sectors. An example of an integrated One Health surveillance network coordinated by the WHO AGISAR group is the tricycle project³⁴. The Global Action Fund for Fungal Infections has provided maps showing availability of key antifungal medicines in each country, how many generic varieties there are, as well as minimum and maximum price³⁵. Further investigation of the antifungal usage, particularly in agricultural settings, is needed on a global scale.

³¹Collignon P, JJ Beggs, TR Walsh, S Gandra. *Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis*. *Lancet Planetary Health*, 2018.

³² <https://ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-and-laboratory-networks/ears-net>

³³ <http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/about-amr/central-asian-and-eastern-european-surveillance-of-antimicrobial-resistance-caesar>

³⁴ Matheu J, A. Aidara-Kane, A. Andremont. *The ESBL tricycle AMR surveillance project: a simple, one health approach to global surveillance*. *AMR Control*, 2017.

³⁵ <https://www.gaffi.org/antifungal-drug-maps/>

Table 2. Major international surveillance networks and systems.

Host	Acronym	Name	Description
European Centre for Disease Prevention and Control (ECDC)	EARS-Net	European Antimicrobial Resistance Surveillance Network	Europe-wide network of national surveillance systems of AMR for seven bacterial pathogens causing invasive infections in humans.
World Health Organization (WHO)	CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance	Network of national AMR surveillance systems including all countries of the WHO European Region that are not part of EARS-Net.
European Centre for Disease Prevention and Control (ECDC)	ESAC-Net	European Surveillance of Antibiotic Consumption Network	Europe-wide network of national surveillance systems, providing European reference data on antimicrobial consumption, both in the community and in the hospital sector.
European Centre for Disease Prevention and Control (ECDC)	HAI-Net	European Healthcare Associated Infections Network	Europe-wide network, coordinating point prevalence survey of HAI and antimicrobial use in acute care hospitals, surveillance of surgical site infections, surveillance of HAI in intensive care units and the repeated prevalence surveys of HAI and antimicrobial use in long-term care facilities.
European Centre for Disease Prevention and Control (ECDC)	FWD-NET	European Food- and Waterborne Diseases and Zoonoses	Surveillance on 21 human diseases acquired through consumption of food or water, or through contact with animals. Parasitic and viral agents are included. AMR data are collected for <i>Salmonella</i> , <i>Campylobacter</i> , and <i>E. coli</i> .
European Medicine Agency (EMA)	ESVAC	European Surveillance of Veterinary Antimicrobial Consumption	Europe-wide network (30 countries) which collects standardised data on the sales of antimicrobial drugs in animals in EU/EEA.
European Food Safety Authority (EFSA)		Network on Antimicrobial Resistance Data Reporting	European network (31 countries) collecting harmonised data on antimicrobial resistance in zoonotic and indicator bacteria from food-producing animals and food in EU/EEA.
World Health Organization (WHO)	GLASS	Global Antimicrobial Resistance Surveillance System	Surveillance of human priority bacterial pathogens considered the greatest threat globally (58 countries included); includes information from other surveillance systems, such as foodborne AMR, monitoring of antimicrobial use and surveillance of HCAI. <i>Candida</i> surveillance is starting in 2020 and data will be collected retrospectively from 2019.

Host	Acronym	Name	Description
WHO AGISAR	Tricycle	One Health Surveillance	Monitoring of ESBL- <i>E. coli</i> in humans, the food-chain and the environment.
Asia Pacific Foundation for Infectious Diseases	ANSORP	Asian Network for Surveillance of Resistant Pathogens	International research group for antimicrobial researchers in the Asian region - consists of over 230 investigators and 123 centres in 14 countries in Asia and the Middle East.
MSD	SMART	Study for Monitoring Antimicrobial Resistance Trends	Monitoring the in vitro susceptibility of clinical bacterial isolates to antimicrobials in intra-abdominal infections worldwide
GSK	SOAR	Survey of antibiotic resistance	Collection of antibiotic surveillance data on the susceptibility of pathogens that cause community-acquired infections in countries where resistance data can be scarce.
Pfizer	ATLAS	Antimicrobial Testing Leadership And Surveillance	Interactive website that provides global AMR surveillance data from 60 countries. Integrates three surveillance programs (TEST: Tigecycline Evaluation and Surveillance Trial, AWARE: Assessing Worldwide Antimicrobial Resistance Evaluation, and INFORM: International Network for Optimal Resistance Monitoring). Generated global bacterial susceptibility data versus a panel of antibiotics from 760 sites in 73 countries.
Wellcome Trust, UK	SEDRIC	Surveillance and Epidemiology of Drug-resistant Infections Consortium	Network of 12 international experts to share expertise and act to tackle the gaps in AMR surveillance and epidemiology, develop guidelines and tools to encourage data sharing, translate scientific evidence into policy.
COMBACTE-Magnet	EPI-Net	Surveillance platform of antimicrobial resistance including human and animal data	Network of surveillance systems, experts and stakeholders collecting resistance data on the WHO priority pathogens for R&D of new antibiotics.
Global Action Fund for Fungal Infections	GAFFI	Surveillance of antifungal use and fungal disease	GAFFI presents burden of disease maps for fungal diseases, fungal allergies and use of antifungals.

Surveillance activities should also include standardised parameters for sample collection and data harmonisation on the prevalence of antimicrobial resistance. This action would enable the estimation of the size of the reservoir of antimicrobial resistant bacteria and fungi outside the hospital environment, and an evidence-based risk assessment that includes a comparative analysis of resistance genes may clarify the extent to which

agricultural and environmental sources of resistant bacteria and fungi contribute to the burden of AMR in humans.

An early warning system at the global level could provide additional information on the link between emerging resistance and pathogenicity and how quickly this resistance would spread throughout bacterial and fungal populations worldwide, if appropriately combined with information on resistance genes. This type of information is pertinent to the development of new antibiotics and antifungals and to refining infection prevention and control measures. Preferably, such a global warning system on AMR should be integrated within existing (inter)national early warning systems on infectious diseases, like the Early Warning and Response System for communicable diseases in the EU/EEA (EWRS)³⁶, Joint FAO/OIE/WHO Global Early Warning System (GLEWS)³⁷, Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)³⁸ and others.

In 2015, WHO held a workshop to identify knowledge gaps and to develop a research agenda for Water, Sanitation and Hygiene (WASH) aspects in combatting AMR³⁹. An environmental surveillance system based on strategic monitoring of resistant *E. coli* was suggested as a simple and feasible method since these bacteria are routinely monitored in drinking water, wastewater and other environmental samples. Therefore, extending such monitoring of AMR in *E. coli* and other coliforms may be possible in existing environmental laboratories as well as in clinical, veterinary and food safety laboratories.

Research and innovation objectives and activities

Improve and standardise AMR surveillance systems, from sampling to data analysis including sampling frame, tools, methodology and reporting

The strengths and weaknesses of the AMR surveillance networks of individual countries, both in Europe and beyond, must be addressed to create (or extend) and extend internationally effective and sustainable surveillance networks. Mapping of these networks is currently ongoing. The needs of different stakeholders regarding surveillance data must to be thoroughly explored to produce guidance on the methodology and best practices to support the standardisation of AMR surveillance systems and to allow for comparison of results across countries and regions. The methods included range from sampling frames (what, when, where and how), sampling techniques and tools, susceptibility testing, (external) quality assurance schemes, data analyses, interpretation, and reporting. Furthermore, capacity building, education and training are also fundamental to build and share knowledge and expertise to ensure that gold standards are implemented and maintained in AMR surveillance across countries. Specific objectives may include the implementation of tools to synthesise traditional

³⁶ <https://ewrs.ecdc.europa.eu/>

³⁷ <http://www.glews.net/>

³⁸ <https://www.glopid-r.org/>

³⁹ Wuijts S, Van den Berg H, Miller J, et al. Towards a research agenda for water, sanitation and antimicrobial resistance. Journal of Water and Health 2017

strategies for AMR surveillance, community and hospital case-based approaches and strategies for sustainable mechanisms of data collection within a One Health Context.

Strengthen the use of surveillance data to identify human and non-human reservoirs of AMR

AMR can accumulate in reservoirs. The role of different reservoirs, and their impact on health, need to be better assessed. Structured surveys and surveillance of environmental habitats should be harmonised by coherent sampling frames and a comparable data structure. Novel technologies that allow accurate detection and prediction of the abundance and diversity of genes comprising the resistome should be further developed.

Surveillance systems in countries include, and sometimes integrate, resistance data and consumption data from separate sources. The optimal strategy for surveillance within a One Health approach needs to be defined. Studies are needed on the contact between different resistance reservoirs, which are designed to define direction and extent of transmission to yield scientific evidence for risk assessment. The relative contribution of selective pressure and spread in different settings also needs to be better defined in relation to risk assessment and risk management. Scientific evidence should be used to create political and public awareness of the importance of managing and limiting the spread of antimicrobial resistance.

Optimise the use of surveillance data to estimate burden and assess the impact of interventions

Efforts are required to design surveillance data collection, especially in LMICs, to assess the impact of interventions and the impact of AMR on One health (burden, transmission, and emergence). Therefore, microbiological information should be linked to clinical and epidemiological data, patient outcome and characteristics, and to similar data from the animal, agricultural and environmental sectors. Surveillance can provide information and a framework on the design and impact of interventions on a population level. Interactive, updated and user-friendly websites, mobile applications and the use of social networks giving rapid access to AMR surveillance data will provide healthcare and animal health professionals, farmers and antimicrobial users with access to point-of-care/point-of-use tools that support improved decision-making. Increased understanding of the estimations of the real burden (in terms of infection, death, cost etc.) associated with AMR worldwide is needed, especially in LMICs where there is a large knowledge gap. Moreover, agricultural and environmental surveillance for antibiotics, antifungals and resistance genes in sewage, water systems, food and agricultural wastes could provide data on antibiotic and antifungal use in humans, animals and farming systems, and when and where these are not well registered (as shown in Global Sewage Project⁴⁰). The global spread of AMR could be monitored in combination with metagenomics analyses.

⁴⁰ <https://www.compare-europe.eu/Library/Global-Sewage-Surveillance-Project>

Develop novel techniques to supplement and promote the exchange of surveillance data

Research infrastructures should be developed and implemented, or further coordinated in the case that they already exist, to facilitate the exchange and integration of surveillance data to perform (inter)national meta-data analysis. There is a need to create, maintain or coordinate open access data warehouses where sequence data can be imported, quality checked, and individual isolates can be put into a global context (for instance by improving bioinformatics pipelines). The issues of confidentiality and of incentives for data sharing should also be considered. Research on novel technologies should determine whether conventional surveillance approaches based on phenotypic characterisation of isolates should be replaced or complemented. Data on antimicrobial surveillance should be linked with information on colonisation, (co-)infection and host factors (such as clinically available information) where appropriate.

Improve and standardise the surveillance of antimicrobial use

Information needs to be collected on the appropriate use of antimicrobials in all One Health domains. In recent years, surveillance systems have been established on the human (ESAC hosted by ECDC)⁴¹ and veterinary consumption (ESVAC hosted by EMA)⁴² of antibiotics in the EU/EEA. Currently, limited surveillance systems exist in the antifungal area, with the exception being surveillance of the healthcare availability of antifungals conducted by GAFFI⁴³. However, accurate and comparable information on antimicrobial use across countries is difficult to obtain as many actors are involved and countries have different regulations and distribution systems. The strengths and weaknesses of such national systems need to be addressed with respect to potential similarities and gaps to aim for harmonisation and standardisation at the international level. Collaborative efforts between private and public bodies are conditional for success in achieving these goals. Furthermore, studies should focus on the illegal trade of antimicrobials to evaluate its magnitude, as well as the supply and delivery routes. This knowledge should aid action against this possibly underestimated aspect of the antibiotic and antifungal consumption in certain countries.

⁴¹ <https://ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-and-laboratory-networks/esac-net>

⁴² http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp

⁴³ www.gaffi.org

Transmission

Understanding and preventing the transmission of antimicrobial resistance

The goal of this priority topic is to study selection and transmission of AMR in a One Health context. Selection and transmission are two different phenomena. Organisms exposed to selectors (e.g. antimicrobials and other biocides, disinfectants and heavy metals) may develop resistance either by gene mutation or by the transfer and acquisition of genetic components from another strain, and thus be “selected” for, in terms of growth, over susceptible strains. Transmission in a One Health context refers to the spread of bacteria and fungi or resistance genes within and between humans, animals and the environment.

Introduction

The dynamics of AMR selection, gene transfer and transmission are complex. Selectors have significant effects on selection and transmission, since transmission of resistance is far more likely to occur under the selective pressure. However, selectors may also differentially affect bacterial and fungal species and mechanisms of resistance providing an evolutionary advantage to strains able to survive antimicrobial concentrations over the epidemiological cut-off value (ECOFFs).

Transfer of genetic material between bacterial populations resulting in new resistant strains, occurs by transformation (the uptake of DNA fragments by bacteria), conjugation (direct transfer of DNA between two organisms through a DNA translocation system), or transduction (transfer of DNA mediated by bacteriophages). Fungi may have inherent or acquired resistance, and can use sexual reproduction, ploidy changes, and genetically stable or unstable changes to adapt to antifungal pressure. Using these processes fungi develop antifungal resistance which can be spread through the population, regionally and globally⁴⁴.

The effects of selectors vary in the different compartments of the human body, due to differences in the concentrations of drugs, competing flora, and host immune factors. For example, an antimicrobial given intravenously may produce levels in the gastrointestinal tract that also promote the selection of resistant bacteria. This may have a considerable effect on the emergence and spread of antimicrobial resistance as the gastrointestinal tract is the main body site where selection for resistance occurs due to high density of microbial populations, and in which resistance genes are exchanged between organisms resulting in new resistant clones. Selection by transfer of genetic resistance elements within and between bacterial and fungal species can also occur in different compartments of the environment, such as in soils, sewage and wastewater, insects and wildlife, and natural aquatic systems, such as near shore ocean waters.

⁴⁴ <https://www.sciencedirect.com/science/article/pii/S1087184519301975?via%3Dihub>

Transmission is greatly influenced by behavioural, cultural and socio-economic aspects, for example handwashing, migration, tourism, companion animals, agricultural practices (e.g. the use of antimicrobials in crop production, and antibiotic use in aquaculture), education, public health and other infrastructures and trade. The gut serves as the main reservoir for resistance from which transmission occurs due to faecal excretion of resistant bacteria. Resistant bacteria may spread in and between farms, through trade networks or the food chain. The release of these bacteria into the environment provides a range of transmission routes for the dissemination and exposure of people and animals, especially when water quality, sanitation and hygiene conditions are poor. Persistent and circulating resistant bacteria in water systems (including wastewater) play an important role in the transmission between environments within countries and across borders. Dissemination of resistant bacterial strains occurs between individuals, at the human population level, within the community, within and between hospital wards, between community and healthcare institutions, and between healthcare settings in different countries. Few fungal infections are transmitted between individuals; however, antifungal resistance can develop within individual susceptible infected hosts. Spread of resistance has been reported between agricultural settings and susceptible individuals.

Challenges

This research priority offers an opportunity to understand the complexity of how resistance is spread to quantify transmission rate, and to identify critical control points at which targeted interventions could substantially reduce the spread of resistance. For example, despite limited knowledge on the transmission of ESBL⁴⁵ between humans, the interventions to control transmission have primarily been tested in hospital settings. However, recent studies have highlighted the transmission of ESBL-producing *E. coli* in the community, possibly by exposure to contaminated food or community sewage and excreta in settings with poor water, sanitation and hygiene conditions.

Transmission within and between One Health reservoirs is still poorly understood. There is a need to design *ad hoc* studies to evaluate and quantify transmission routes. The different routes of transmission between reservoirs and their associated burden should be studied epidemiologically to trace bacteria, fungi and resistance genes from one reservoir to another. Efforts should be directed at quantifying the potential risk of food, wastewater and waste materials as vehicles for resistance genes and resistant bacteria and fungi.

Quantitative methods and adapted study designs are still lacking to identify and characterise the genetic, nutritional, and population determinants that contribute to the spread of resistance in and between different reservoirs (including livestock, crops, healthy populations, patients, and the environment). Disciplines, including veterinary, clinical, farming, environmental, statistical and modelling, microbiological, and epidemiological sciences, need to work together, in a One Health context, in order to identify the hotspots of resistance spread and emergence. It is of particular interest to

⁴⁵ Extended Spectrum Beta Lactamases (ESBLs) are enzymes made by bacteria that make them resistant to almost all kinds of beta-lactam antibiotic, except for carbapenems and cephamycin.

gauge the contribution of the large veterinary, agricultural and environmental reservoirs of antimicrobial-resistant organisms to resistance in humans and the role that food, air and water may have in transferring resistance genes and antimicrobial-resistant bacteria and fungi. This is a topic of considerable debate, but few studies have been conducted to indicate causality and directionality of spread of resistance genes between human, animal and environmental reservoirs.

The dynamics of resistance genes in the microbiota of humans, animals and environmental sources, and how these genes can transfer between the different bacteria and fungi, also need to be studied. It is of crucial importance to understand fitness costs of different resistance mechanisms, their retention in the absence of selection as well as their evolution in different contexts. Epidemiological studies on the effects of selectors on transmission are required.

Understanding transmission will have a profound impact on the optimisation of the measures that can be taken to limit the spread of resistant bacteria and fungi. A relatively understudied subject in the spread of antimicrobial resistance is the assessment of the impact of international networks of healthcare in which patients are moved between healthcare providers. The assembly of a European Health Care Utilisation Atlas (European Collaboration on Healthcare Optimisation)⁴⁶ may provide guidance for policy decisions and an objective assessment of the influence of the EU directive of patient rights to cross-border healthcare. It will also be possible to appraise the role of primary healthcare as gatekeepers to hospital admissions. Such evidence will increase the understanding of the transmission dynamics of antimicrobial resistance and how this transmission can be efficiently curtailed by the development and use of evidence-based interventions.

Research and innovation objectives and activities

Unravel the complex dynamics of selection and transmission of antimicrobial resistance

Multidisciplinary research networks, combining for example clinical and veterinary scientists, microbiologists, ecologists, mathematical modellers and epidemiologists, are needed to conduct collaborative and complementary studies that will unravel the dynamics of selection and transmission of AMR. These studies should provide a better understanding of the mechanisms that contribute to the spread of AMR in populations, which will provide testable hypotheses and risk assessment for interventions aimed at reducing the emergence and spread. The study of AMR transmission must be conducted in appropriate settings but should also consider the broader One Health context.

Identify factors responsible for the persistence and spread of resistant organisms and resistance elements

Factors accounting for the success of clones, organisms, and resistance elements must be investigated to explain the epidemicity of antimicrobial resistant strains. Such studies should identify events and factors that account for the persistence and spread of

⁴⁶ http://www.euro.who.int/_data/assets/pdf_file/0011/97598/E91713.pdf

resistant organisms and genetic determinants. Selection and transmission within and between individuals, and between human and non-human sources need to be studied. The effectiveness and magnitude of the transmission of resistant bacteria and fungi and the transfer of genetic elements along the food chain and in the environment, in One Health, need to be documented to be able to identify critical control points of this transfer and transmission. In addition, the impact of different concentrations and mixtures of antimicrobials, including the impact of different hosts and microbiomes, need to be studied with respect to selection, transfer and transmission of AMR. Novel methodological techniques (combining genomic and metagenomic techniques with machine learning, mathematical modelling, network analysis, and big data) can be used to determine the success and abundance of antimicrobial resistant bacterial and fungal strains through the development of risk assessment approaches that are based on the genomic repertoire of bacterial and fungal pathogens and the ecological constraints that determine their fitness in clinical, community, veterinary, agricultural and environmental settings.

Determine the impact on AMR of different systems of healthcare, animal production, global trade, and environmental pollution and contamination

Different global healthcare systems, facilitating or inhibiting the expansion of AMR, should be compared. In addition, data on the role of migration, tourism, the organisation of healthcare, farming and agricultural practices (including animal transport) and management of human and animal wastes on the dissemination of AMR need to be explored with consideration of circular economy. An integration of biological, environmental, sociological, epidemiological and economic data will identify the important drivers of exposure of humans to selectors and AMR genes. Inherent to this analysis is the mapping of the distribution of strains and plasmids of public health importance, which will generate the contextual evidence for the association between healthcare networks, food production, trade, infrastructure and certain genomic lineages of important nosocomial pathogens. This information may be translated into policy measures to control the emergence and spread of antimicrobial resistant bacteria and fungi in countries.

Environment

The role of the environment in the persistence, selection and spread of antimicrobial resistance

The goal of this priority topic is to investigate the effect of antimicrobials, antimicrobial residues and biocides in the environment on the persistence and selection of AMR, and the role of the environment for the transmission of resistant bacteria, fungi and resistance genes to assess its impact on the health of humans, animals, plants and ecosystems. It is important to estimate the risk of emergence of AMR from human and animal waste sources and agricultural practices and to quantify human and animal exposure to AMR from food, feed, air and water. Insights into the role of the environment in the development, selection and spread of AMR should lead to the establishment of effective management guidelines and to the development of technical as well as socio-behavioural interventions.

Introduction

Transmission and development of antimicrobial resistant organisms and their evolution occurs in the environment. The environment is exposed to residues of antimicrobials (antibiotics, antifungals, heavy metals, biocides and other drugs), antimicrobial resistance genes and antimicrobial resistant bacteria and fungi. Direct release of human and animal excreta, sewage, compost, wastewater from pharmaceutical industry and healthcare settings, agricultural and aquaculture systems, and sudden release of antimicrobials by accident contribute to the emergence and spread of AMR in the environment. Similarly, the application of antifungals in crop treatments, and the interplay between the resistance or susceptibility of crops to fungal disease and antifungal use in agriculture, leading to clinical antifungal resistance should be acknowledged. Co-selection for AMR in a wastewater community or agricultural setting can occur at low antimicrobial concentrations and where multiple selectors are present.

In many countries, human sewage is not collected and physically and biologically treated/disinfected or otherwise subjected to advanced wastewater management. Faecal contamination is a major factor in the contamination of food and water, particularly in resource-limited settings. Rivers and other bodies of water can be contaminated with human sewage and animal agricultural wastes, but data on environmental contamination by antimicrobial residues and faecal bacteria or fungi carrying resistance genes through sewage or run-off sources is scattered. As water bodies can transport antimicrobial resistant bacteria and fungi rapidly over long distances, and become reservoirs for both vertical and horizontal gene transfer, the emergence of new resistant microbes and uncontrolled pollution constitutes a grave health concern. Farming by-products can contain large amounts of antifungals that were used to treat crops. If composting practices do not ensure complete breakdown of the antifungal compounds release of these agents to the environment will occur.

EU policies (e.g. on nutrients and surface water quality) have contributed to relatively high water quality in most EU/EEA countries. However, the effectiveness of waste management options with respect to the emergence and spread of AMR is largely unclear. Existing policies are not sufficient to ensure the systematic reduction of resistance genes and mobile genetic elements from treated water. In contrast, in other regions, treatment of human, animal and agricultural waste is still inadequate. New global indicators for drinking water, sanitation and hygiene have been developed to prevent recontamination. Access to effective WASH measures and treatment of both animal and human waste to prevent contamination is essential in lowering the burden of disease. This remains an urgent concern and innovative and economically favourable strategies to improve sanitation, without encouraging the development and transmission of resistance, are needed.

Risk factors for the environmental dissemination of AMR have not been adequately assessed. Small point-prevalence surveys have so far lacked the scope to identify risk factors, prevention and control measures, or assess human health risks. A systematic analysis of the contamination of food, other than meat, is still lacking. It is currently unknown to what extent food carries resistant bacteria and if and how these bacteria may colonise healthy individuals. Global trade and the increasing import of food products pose additional risks of the import of multi-drug resistant and extensively-drug resistant organisms.

Although water, wastewater, manure, compost and sewage treatments are being piloted in areas lacking sanitation, there are no systematic programmes that address the impact of these treatments on AMR in the environment. Reducing the load of resistance released into the environment would significantly decrease the burden of resistant bacteria and fungi in all One Health settings, and thereby reduce the impact of AMR on public health.

Challenges

The hydrological cycle is central to the spread of AMR since it connects people, animals and the environment. Manure, human waste and crop waste may run-off to surface and ground water during precipitation events. It is estimated that over 80% of the human excreta and wastewater generated globally is discharged into surface waters without treatment. One Health research on the decontamination of wastewater, human and animal excretions, cropping by-products and sewage, taking into account co-benefits and side-effects remains scarce. Different existing wastewater, compost and excreta treatment technologies should be explored taking into account robustness, cost-effectiveness and sustainability. New sanitation concepts such as community-led total sanitation should be explored with respect to best practices e.g. for waste management in rural areas.

A comprehensive human health risk assessment of the burden associated with AMR in the environment is needed, to address AMR as a serious health risk associated with water, sanitation and hygiene. Hazard identification, exposure assessment, health impact assessment and risk characterisation may contribute to a quantitative risk assessment and identify new opportunities for prevention and intervention measures

to control AMR. Research should elucidate how the complex interplay between the major elements in the environment (residues, naturally resistant microbes, and bacteria and fungi with acquired resistance) contribute to the global burden of AMR.

The attributional proportion of the recontamination of humans and animals with resistant bacteria and fungi via the surrounding environment remains undetermined. Risk assessment studies are needed to estimate the proportional contribution of AMR from different sources and reservoirs, the disease burden, and impact on environmental transmission pathways.

Innovative research and development will result in better control of AMR and will generate economic benefits. Improved international collaboration is needed to support the development and implementation of novel, low-tech and low-cost procedures for environmental decontamination. This is particularly relevant for LMICs.

The Joint Monitoring Programme for Water Supply and Sanitation⁴⁷ has been monitoring progress on drinking water and sanitation since 1990 and is collaborating with UN-Water partners to develop a framework for integrated monitoring of water and sanitation related to the SDG targets under the recently established Global Expanded Monitoring Initiative⁴⁸. It is timely and appropriate to encourage the monitoring of antimicrobial resistant "indicator" organisms and their resistance genes in this global monitoring programme. WHO, through its Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)⁴⁹ program, has initiated recently the One Health monitoring of ESBL *E. coli* in clinical, animal, agricultural and environmental samples through its so-called Tricycle project. The impact of different farming practices and settings on the emergence, transmission and persistence of AMR needs to be assessed.

Research and innovation objectives and activities

Determine and model the contribution of contamination sources, environmental reservoirs and exposure routes on the emergence and spread of AMR

Assessment of the role of different sources, reservoirs and exposure routes is needed to estimate the proportional attributions of the various selectors and reservoirs on the transmission of AMR to and from the environment, animals and humans. This includes the development and implementation of systematic and consistent monitoring systems, data analyses and models appropriate to take into account the environment as an important One Health reservoir. The assessment can also be used in mathematical modelling to study the impact of prevention and intervention measures to reduce AMR.

⁴⁷ http://www.unwater.org/publication_categories/whounicef-joint-monitoring-programme-for-water-supply-sanitation-hygiene-jmp/

⁴⁸ <http://www.unepdhi.org/whatwedo/gemi>

⁴⁹ http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/agisar/en/

Evaluate the relationship between AMR and the environment, climate change, and pollution

More research is needed to define the burden of AMR in the environment. The evaluation of existing methods and the development of novel methods and protocols is needed to assess the presence of AMR in the currently changing environment with respect to climate change, unforeseen events and pollution.

Assess the potential impact of industrial systems on AMR in the environment

Applied research should stimulate the adaptation of industrial systems (e.g. antimicrobial manufacturing, agricultural and aquaculture systems, healthcare facilities) to reduce AMR in the environment. Such procedures include:

- Development of methods and/or policies to reduce the discharge of antimicrobials and residues, as well as resistant bacteria and fungi, and their genes;
- Improvement of sewage and wastewater treatments from industries, healthcare facilities and the general community to reduce the environmental concentration of antimicrobials, resistant bacteria, fungi and their genes;
- Development of novel bio-engineering methods to minimise the release and spread of AMR in the environment.

New industrial methods to reduce and prevent additional contamination of the environment with resistant bacteria, fungi and antimicrobial residues could best be developed in partnership between academia and bio-sanitation engineering industries.

Develop innovative technological, policy, social, economic and regulatory approaches to mitigate AMR in the environment

To be able to identify, assess, develop and implement effective prevention and intervention measures, it is necessary to identify the hazards (or health risks) of antimicrobials and antimicrobial resistant bacteria and fungi in environmental ecosystems. This includes the identification of hotspots for antibiotic and antifungal resistance, and regulation of antimicrobial use, including the use of antifungals in agriculture. Systematic and consistent monitoring systems will help to assess the prevalence of AMR in the environment, determine the incremental health risks of AMR bacteria and fungi caused by environmental exposures and then characterise these risks as risk assessments. This will provide input for the development of integrated technological, policy, social, economic and regulatory approaches to identify the conditions of greatest risk and identify the most effective interventions and their management systems that could reduce AMR in a One Health framework.

Interventions

Investigation and improvement of infection prevention and control measures in One Health settings

The goal of this topic is to construct interventions reducing the emergence and spread of AMR through prevention and control of AMR and prudent use of antimicrobials. In this context, interventions refer to all strategies, tools, and actions used to reduce and prevent the emergence, transmission, and infection of organisms by infection control and the promotion of responsible and prudent use of antimicrobials by antimicrobial stewardship.

Introduction

In order to prolong the usefulness of existing and new drugs towards infectious organisms, effective and validated interventions should be implemented to prevent or minimise the spread of infections and the misuse of antimicrobials in clinical and veterinary medicine, agriculture, aquaculture and food production. To develop cost-effective interventions, more knowledge about the acquisition, occurrence, and transmission pathways of AMR with full consideration of a One Health perspective is needed. Despite the acknowledgement of the importance of raising the awareness of the AMR threat among antibiotic producers, prescribers, users and consumers, successful campaigns are generally not further developed or shared to maximise impact. Uptake of evidence-based infection prevention and control measures, and the use of technological innovations for decontamination after outbreaks or protection of the environment, is slow. As the introduction and use of new interventions are hampered by different economic, cultural, contextual, and behavioural determinants, the strategies to tackle these barriers need to be equally diverse and should be adapted to their use in all One Health settings.

Several recent reports on the AMR threat have highlighted the importance of behavioural and technological interventions for improving the health and wellbeing of populations, such as processes to clean water and improvements in hygiene and sanitation. These interventions are viewed as crucial for general infection prevention and control, as well as the spread of AMR, both in human and animal health. Special emphasis should also be placed on improved methods to raise awareness about the threats related to AMR and individual roles in addressing AMR as a global issue.

Research into interventions and implementation strategies is important to develop recommendations for national and international antimicrobial use and infection prevention and control guidelines. Assessment of the usefulness and cost-effectiveness of new recommendations should be of value for those in charge of infection prevention and control, and antimicrobial stewardship in One Health. Ultimately, this research will contribute to the prevention of drug-resistant infections, improved quality of human and animal healthcare, improved patient safety and biosecurity, and global environmental protection.

Challenges

This research priority offers many important starting points for future research activities, technical innovations and behavioural studies, which could be useful for those in industry, healthcare management, health insurance companies, veterinary medicine, farming and in environmental protection. The assessment of strategies to guide behavioural changes that modify perceptions and compliance of, for example, guidelines and recommendations, could offer cost-effective solutions to pressing needs in infection prevention and control, and antimicrobial stewardship. More studies are needed on the socio-economic contexts and conditions determining antimicrobial use.

Improving and modifying perceptions, compliance and education of patients and healthcare workers is crucial to reduce the burden of infections in human health and community care. Cost-effective interventions such as new digital devices and platforms, e-health systems, and other technological innovations must be developed and introduced to monitor prescription practices, compliance, healthcare worker-patient contact, and staff-patient-equipment logistics in the context of general patient and hospital management. Healthcare systems in resource-poor settings are in dire need of improved technologies for diagnosing and treating infectious disease. Adapted preventive measures and interventions to reduce the emergence and transmission of AMR, as well as access to the appropriate antibiotics and antifungals for treatment of infections is equally important.

The need to introduce new evidence-based interventions is particularly evident in veterinary medicine and farming, which has few prospects for the introduction of treatment options based on new antimicrobials. Instead, new farming and production methods, and other interventions improving hygiene and living conditions of livestock, as well as treatment of crops, may prevent infectious diseases and reduce the need for antimicrobial use without threatening food production or economic profitability. The successful introduction of interventions depends on complex relations between the awareness and acceptance by producers, farmers and consumers, the use of financial incentives, and introduction of regulation, oversight and sanctions. The impact of these interventions will depend on societal costs in terms of yield, animal health and welfare, and development of resistance affecting human health. More research is needed to identify the most appropriate and efficient approaches to implement antimicrobial stewardship or benchmarking in countries with diverse agricultural production systems and livestock populations.

Interventions are needed to protect humans and animals from infectious organisms originating in the environment and to prevent the contamination of the environment by antimicrobial agents. Strategies and methods to define and measure acceptable emission levels and environmental quality standards for selective agents and resistant bacteria and fungi must be developed to guide interventions such as management of wastewater, sewage, agricultural and industrial discharges. Identifying which technological, socio-economic and behavioural interventions that can most effectively mitigate the emergence and spread of antimicrobial resistance via the environment is a key challenge that requires attention at both policy and research level.

There have been numerous campaigns to promote the prudent use of antimicrobials, varying from simple, low-cost internet campaigns to expensive mass-media campaigns. The capacity of these individual campaigns to affect behavioural change and how these campaigns affect the development of resistance to antimicrobials is difficult to assess. The collective approach of social media and communication campaigns, simultaneously targeting physicians, veterinarians, farmers and the public with multiple interventions, makes it difficult to establish which strategy is most efficient in changing attitudes, beliefs, norms and practices. Further research is needed, particularly in resource-poor settings, to determine the impact of information, training and public campaigns on the emergence and spread of AMR, and on the level of awareness and public perception of the AMR issue.

Research and innovation objectives and activities

Develop innovative interventions aimed to detect, prevent and control the spread of AMR in a One Health perspective

While studies evaluating the uptake and compliance of existing interventions are important, the development of novel and innovative interventions are needed to better detect, prevent and control the spread of AMR in a cost-effective way. Technologies based on nano-active or antimicrobial materials, phage therapy, and innovative cleaning strategies for hospitals, farms and environmental reservoirs (e.g. wastewater treatment plants), and strategies to block gene transfer (e.g. conjugation inhibitors) are just some examples of innovative interventions that could prevent the spread of AMR. Interventions such as interactive journaling and decision support systems that improve feedback, communication and collaboration between healthcare professionals, veterinarians, farmers and other users of antimicrobials, may help to improve antibiotic and antifungal prescription behaviour and the responsible and prudent use of these drugs.

Investigate the effectiveness of AMR prevention and control strategies to increase uptake and acceptance in One Health settings

Uptake and acceptance of prevention and control strategies in One Health settings need to be analysed with respect to economic conditions and the social and cultural context. Economical, sociological, and anthropological empirical studies are needed. In addition, well-designed multicentre prospective intervention trials are needed to establish the effectiveness of AMR infection prevention and control strategies. Cluster-randomised studies, in which groups of subjects are randomly allocated to interventions, have emerged as an appropriate study design, although they require significant resources and a broad partnership of organisations and investigators to yield useful results. Cluster-randomised studies that involve a large, heterogeneous set of hospitals, healthy humans, and clinical, veterinary or environmental settings may yield more generalisable and relevant results than a randomised trial in a single location.

Assess the effectiveness and cost-effectiveness of specific AMR prevention and control practices, considering different geographic and socio-economic settings

Identification of the most appropriate and effective infection prevention and control measures and antimicrobial stewardship interventions tailored at different geographic, cultural and socio-economic societies is necessary to contribute to the reduction of AMR. In resource-poor settings, the high endemicity of antibiotic resistance is of concern, and the situation concerning antifungal resistance is unknown. Tailored infection prevention and control strategies, as well as basic but adequate surveillance systems and improved access to accurate diagnostics, need to be developed and implemented. The introduction of interventions into any setting must consider the needs of individual societies and cultures in order to be effective, and a 'one size fits all' approach is unlikely to reduce the global burden of AMR. The cultural aspects of implementing interventions, differences in resistance and infection patterns, and the economic capacity to bear the cost of interventions must be considered when developing, implementing and evaluating new interventions for different settings.

Optimise implementation strategies, including drivers for and barriers to behavioural change, to reduce AMR

Drivers and barriers to behavioural change need to be studied to determine why there are different levels of awareness and perception among producers, prescribers, users and consumers of antimicrobials. Implementation of best practices, using quality improvement methods or clinical algorithm testing strategies (e.g. small-scale interventions for infection prevention and control and interventions for agricultural antifungal use) need to be evaluated. Cross-sectional surveys to assess the quality and effects of implementation strategies (such as education, role models etc.) on promoting the prudent use of antimicrobials in various settings and countries are required. It is also important to understand better why previous implementation strategies have failed to be effective.

Understand the prescription behaviours contributing to the responsible and prudent use of antimicrobials

It is important to further understand the behavioural process of antibiotic and antifungal prescribing in order to contribute to optimisation of (empiric) antimicrobial therapy. Different factors associated with inappropriate use include lack of knowledge and awareness of the issue of AMR, and the attitude and behaviour of the individual prescribing physician/veterinarian/farmer. Consequently, research on healthcare, public health, veterinary, and farming systems are essential to improve professional development and train prescribers and users, together with improving the community-level understanding, to ensure minimal consumption of antimicrobials.

Assess educational and training programmes to enhance antimicrobial awareness and stewardship

Educational campaigns and training programmes to promote the prudent use of antibiotics and antifungals is a key intervention measure to enhance stewardship. It is important to raise the awareness of the burden of antimicrobial resistance among

physicians. Campaigns can vary from simple, low-cost internet campaigns to expensive mass-media campaigns aiming to affect behavioural change in diverse target groups such as physicians, veterinarians, farmers and the public. Campaigns may apply multiple simultaneous interventions making it difficult to establish which strategy is most efficient in changing attitudes, beliefs, norms and practices. Further research should assess the impact of information, training and public campaigns on the development of resistance to antimicrobials and the general public awareness of the AMR issue over time, particularly in resource-poor settings.

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- JPIAMR Scientific Advisory Board
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- JPIAMR Steering Committee
- JPIAMR Management Board
- Consulted experts
- The Netherlands Organisation for Health Research and Development
- The JPIAMR Secretariat
- The Antifungal Advisory Group

Appendix I. Update process of the Strategic Research and Innovation Agenda

Process for update

The JPIAMR Management Board took the decision to update the SRA. A first workshop was held in December 2017 with the members of the JPIAMR Scientific Advisory Board to review the Strategic Research Agenda to identify gaps across the priority topics. An Editorial Board was established from the JPIAMR members. Below are the key elements of the process to update the SRA into the new SRIA:

- Three consultation rounds with the JPIAMR Scientific Advisory Board (November 2016; April 2018; December 2018).
- Four meetings with the members of the Editorial Board (February 2017; June 2018; October 2018; December 2018).
- Monthly telephone conferences with the members of the Editorial Board.
- Consultation with the JPIAMR member countries (July 2018 – September 2018).
- An online open consultation (July 2018 – September 2018).
- Consultation with the JPIAMR Steering Committee and JPIAMR Management Board (March 2018; October 2018).
- A stakeholder consultation organised by the JPIAMR secretariat (December 2018).
- The formal SRIA adoption took place in the JPIAMR Management Board in March 2019.
- Antifungal consultations with experts in June/July 2020.
- Open and JPIAMR member country consultations on the antifungal broadening (November 2020 – December 2020).

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Appendix II. Abbreviations

AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMR	Antimicrobial Resistance
ANSORP	Asian Network for Surveillance of Resistant Pathogens
ATLAS	Antimicrobial Testing Leadership and Surveillance
AWARE	Assessing Worldwide Antimicrobial Resistance Evaluation
BEAM	Biotech companies in Europe combating Antimicrobial Resistance Alliance
<i>C. difficile</i>	<i>Clostridium difficile</i>
CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance network
CARB-X	Combating Antibiotic Resistant Bacteria
DNA	Deoxyribonucleic acid
DRIVE-AB	Driving reinvestment in research and development and responsible antibiotic use
<i>E. coli</i>	<i>Escherichia coli</i>
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ENABLE	European Gram-negative Antibacterial Engine
ESAC-Net	European Surveillance of Antibiotic Consumption Network
ESBL	Extended Spectrum Beta-Lactamase
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU InnovFin	EU Finance for Innovators
EU	European Union
EWRS	Early Warning and Response System for communicable diseases in the EU/EEA
FAO	Food and Agriculture Organisation of the UN
FDA	US Food and Drug Administration
FWD-Net	European Food- and Waterborne Diseases and Zoonosis network
GAFFI	Global Action Fund for Fungal Infections
GAP	Global Action Plan
GARDP	Global Antibiotic Research and Development Partnership
GLASS	Global Antimicrobial Resistance Surveillance System
GLEWS	Global Early Warning System
GLOPID-R	Global Research Collaboration for Infectious Disease Preparedness
HAI-Net	European Healthcare Associated Infections Network

HIV/AIDS	Human Immunodeficiency virus/Acquired immune deficiency syndrome
IACG	Interagency Coordination Group on AMR
IMI	Innovative Medicines Initiative
JANIS	Japan Nosocomial Infections Surveillance
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LMICs	Low and middle-income countries
ND4BB	New Drugs for Bad Bugs
Novo-REPAIR	Novo REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund
NTE	New Therapeutic Entity
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
PK-PD	Pharmacokinetics and Pharmacodynamics
PPP	Public Private Partnership
PRIME	Priority Medicines
R&D	Research and Development
RNA	Ribonucleic acid
SDG	Sustainable Development Goals
SEDRIC	Surveillance and Epidemiology of Drug-resistant Infections Consortium
SME	Small and Medium Enterprise
SRA	Strategic Research Agenda
SRIA	Strategic Research and Innovation Agenda
TB	Tuberculosis
TEST	Tigecycline Evaluation and Surveillance Trial
UK	United Kingdom
UN	United Nations
WASH	Water, Sanitation and Hygiene
WHO	World Health Organization

