Research and Innovation Objectives of the One Health AMR Partnership

Draft document December 2022

JPIAMR Secretariat
Swedish Research Council
Box 1035
SE-101 38 Stockholm

www.ohamr.eu
secretariat.jpiamr@vr.se
+46 8 546 44 000

DESIGN OH AMR

Contents

Introduction

What is Antimicrobial Resistance?

Antimicrobials are defined as all compounds that, at low concentrations, kill or inhibit the growth of microorganisms. They can be divided into groups based on the organisms that they target. Antibacterials, commonly known as antibiotics, act on bacteria, whereas antifungals act on fungi, including moulds and yeasts. Other antimicrobials include antivirals and antiparasitics.

Antimicrobial resistance (AMR)[1] is defined as the ability of a microorganism to survive and grow in the presence of antimicrobials. Resistance is generated through genetic modifications including acquisition of resistance genes through horizontal gene transfer or, gene mutations. Due to antimicrobial resistance, antimicrobials used to treat diseases are no longer effective. The presence of the antimicrobial exerts selection pressure for the development of antimicrobial resistance. These resistant microorganisms can then spread more widely within a population, or to other populations or environments.

Unfortunately, the discovery and development of novel antibiotics and antifungals has slowed down, while antimicrobial resistance has increased. The routine use of antimicrobials in human health, companion animals, food animals and crop production contributes significantly to AMR development. 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; stewardship, prudent, rational use of antimicrobials using a One Health approach; and the diagnosis and surveillance of antimicrobial resistant microorganisms and antimicrobial use, are vital in order to develop a global solution to this issue.

The tremendous impact of Antimicrobial Resistance on global health and economy

AMR is a global health challenge that threatens advances in modern medicine. Since the initial discovery of antibiotics 90 years ago, antimicrobials have saved millions of lives, including previously common deaths associated with childbirth, routine surgeries and minor wounds. Modern medicine is reliant on antimicrobials to prevent infections that can occur due to immunosuppression in patients undergoing organ transplant or cancer treatment.

Over the past decade, AMR has been recognised as a critical issue. The World Health Organization (WHO) recognizes AMR as one of the greatest threats to public health. A Global Action Plan to combat AMR[2] was endorsed in 2015. Since then, AMR has risen to the top of the global health agenda with many institutions weighing in, including the UN Environment Assembly, the Council of the European Union[3], the G7[4], the G20[5], the

[1] List of the acronyms and their signification can be found in Annex I.
[2] World Health Organization (2015); Global Action Plan on Antimicrobial Resistance; ISBN: 9789241509763
[3] Council of the EU; Press release (17 June 2016)
[4] G7 health ministers; Communiqué (5-6 November 2017)
[5] G20 Health Ministers; Communiqué (19-20 May 2017)

European Union[6] and the UN General Assembly[7], that led to the setup of the UN Interagency Coordination Group on Antimicrobial Resistance (IACG)[8].

Several studies have attempted to investigate the impact of AMR by examining the effect on health and the cost of AMR to society.[9,10,11] Murray et al,[10] estimated that 1,27 million deaths were attributable worldwide to infections caused by bacterial AMR in 2019. Six pathogens (*Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa*) were responsible for more than 70% of the deaths attributable to infections caused by bacterial AMR. The burden of bacterial AMR is unequal and disproportionally high in Sub-Saharan Africa and South Asia. The burden is also alarmingly high in Europe (in particular in Eastern and Central Europe). The burden of resistant bacterial infections in the European Union and the European Economic Area (EU/EEA) is comparable to that of influenza, tuberculosis and HIV/AIDS combined[11]. The O'Neill[9] report argued that AMR could kill 10 million people per year by 2050 without any prevention and mitigation measures. 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 on healthcare alone.[12] According to the World Bank[13], the economic impact of drug resistance could be as high as a 3.8% loss of global gross domestic product worldwide, including a 7.5% decrease in livestock output. 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.

The impact of antifungal, antiparasitic, and antiviral resistance on human health is for the moment more difficult to quantify than antibacterial resistance, mainly due to the lack of robust surveillance data worldwide, and to the absence of suitable diagnostic tests which reliably identify the aetiology of an infection. However, fungal drug resistance is already perceived as a major threat to public health[14] and there is growing evidence for an increasing rate in antiparasitic and antiviral resistance suggesting that these issues may be of major concern for public health in the coming years, directly on human health, or indirectly, through their impact on the livestock production.

How could Research and Innovation bring solutions to tackle Antimicrobial Resistance

In June 2017, the European Commission (EC) adopted the "EU One Health Action Plan against AMR"[6] to address the emergency of antimicrobial resistance and its

[6] European Commission, Action Plan adopted on 29 June 2017
[7] United Nations General Assembly, Member States, Communiqué (21 September 2016)
[8] United Nations General Assembly, Member States, Resolution A/RES/71/3, paragraph 15 of the Political Declaration
[9] O'Neill, J. (2014) Antimicrobial Resistance, *Tackling a Crisis for the Health and Wealth of Nations.*
[10] Murray C.J.L et al. (2022), *Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis*; DOI: 10.1016/S0140-6736(21)02724-0
[11] Cassini A.M.D (2018), *Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis*; DOI: 10.1016/S1473-3099(18)30605-4
[12] OCDE (2018); *Stemming the Superbug Tide;* doi: 10.1787/9789264307599
[13] World Bank (2017)*; Drug-Resistant Infections: A Threat to Our Economic Future*
[14] Kohlenberg A. (2022), *Increasing number of cases and outbreaks caused by Candida auris in the EU/EEA, 2020 to 2021; DOI: 10.2807/1560-7917.ES.2022.27.46.2200846*

consequences on public health. ”Boosting research, development and innovation” is one of the three main objectives of this action plan. Different partnerships and actions will contribute to achieve this objective in the framework of the Horizon Europe Program. Among those partnerships, the candidate partnership One Health AMR should play a crucial role, supporting research and innovation from the research stages of academic or clinical research to the first steps of innovation and early clinical development.[15] The partnership is scheduled to last for seven years and will aim to:

- Improve the understanding of AMR (identification of novel mechanisms of resistance, characterisation of the transmission routes, including social factors, and evolution of the resistance)
- Prevent the development and spread of AMR (design of preventive interventions, improvement and development of surveillance systems, and development of diagnostic tools and treatment selection solutions)
- Tackle AMR (development of new antimicrobials and novel therapeutics solutions, design of interventions to mitigate AMR, including the development and test of stewardship protocols to control AMR)

The following chapters of this document will describe the research and innovation objectives that the One Health AMR partnership will use to curb antimicrobial resistance through the support of the researchers working on those issues. Those objectives were derived from a series of consultations organised from March 2022 to June 2022 in the framework of the CSA DESIGN OH AMR[16] (Annex II).

The objectives have been organised under five thematic areas: Therapeutics, Diagnostics, Surveillance, Transmission and Evolution, and Interventions for prevention and mitigation. Links to other sections of the document have been included where objectives span more than one area (overlapping objectives).

[15] Please note that the different partnerships will have complementary focus. You can consult the research and innovation priorities of the other programs and initiatives for more information.
[16] JPIAMR Website, https://www.jpiamr.eu/activities/one-health-amr/

Table 1. An overview of the 17 research and innovation objectives from the 5 thematic areas: Therapeutics, Diagnostics, Surveillance, Transmission and Evolution, and Interventions for prevention and mitigation. The objectives within a thematic areas are organised in a logical way (from less applied to more applied science). The numbering does not refer to the relative importance of the objectives.

Thematic Area	Research and Innovation Objectives
Therapeutics	1. Identify new antimicrobials, novel alternatives for antimicrobials, and improved delivery methods 2. Unlock the unexplored potential of existing and neglected antimicrobials by improving PK/PD and enabling repurposing and combination therapies 3. Develop methods to facilitate the approval and registration of new antimicrobial agents or novel therapeutic strategies 4. Develop strategies to minimise the structural and economic barriers to research, development, availability of and access to new therapies and alternative therapeutic strategies
Diagnostics	1. Discover, design, and evaluate new diagnostics and improve the efficacy of existing ones. 2. Evaluate field performance, feasibility and impact of diagnostics 3. Identify and overcome barriers for implementation and acceptance of diagnostics
Surveillance	1. Optimise, standardise, and harmonise AMR & antimicrobial use/antimicrobial consumption surveillance protocols to achieve or improve cross-compatibility of surveillance systems 2. Identify reservoirs and transmission pathways of AMR in and between humans, animals and the environment to enable risk assessment and guide preventative actions 3. Optimise the use of surveillance data to estimate the burden of resistance, assess the impact of interventions and enable policy and practice action 4. Develop strategies and methods to promote the exchange, interpretation and communication of surveillance data
Transmission & Evolution	1. Identify the main environments, mechanisms and drivers involved in the emergence of successful antimicrobial-resistant genotypes of different disease-causing microorganisms 2. Understand the directionality and scale of transmission of resistant microorganisms in and between humans, animals, and the environment, and identify critical routes and underlying drivers of transmission 3. Identify, design and evaluate technical and social interventions to control the emergence and transmission of resistance based on an understanding of the relative importance of different sources and drivers
Interventions for prevention & mitigation	1. Evaluate opportunities, acceptability and feasibility of interventions in different countries/local contexts 2. Design and test interventions based on new and existing evidence and new technologies to prevent and mitigate AMR 3. Estimate the impact and cost-effectiveness of new interventions and prevention strategies 4. Identify the parameters that should be considered to adapt a successful intervention to different settings, or to scale up interventions

Considering the complexity of AMR, some specific issues will be applicable to all the thematic areas. Those cross-cutting issues are expected to be taken into account in the design, development and implementation of the research for each of the areas. The cross-cutting issues are:

- Social Sciences
- Implementation Science
- Innovation
- Globalisation

Crosscutting issues will be described into more detailed in the last section of this document.

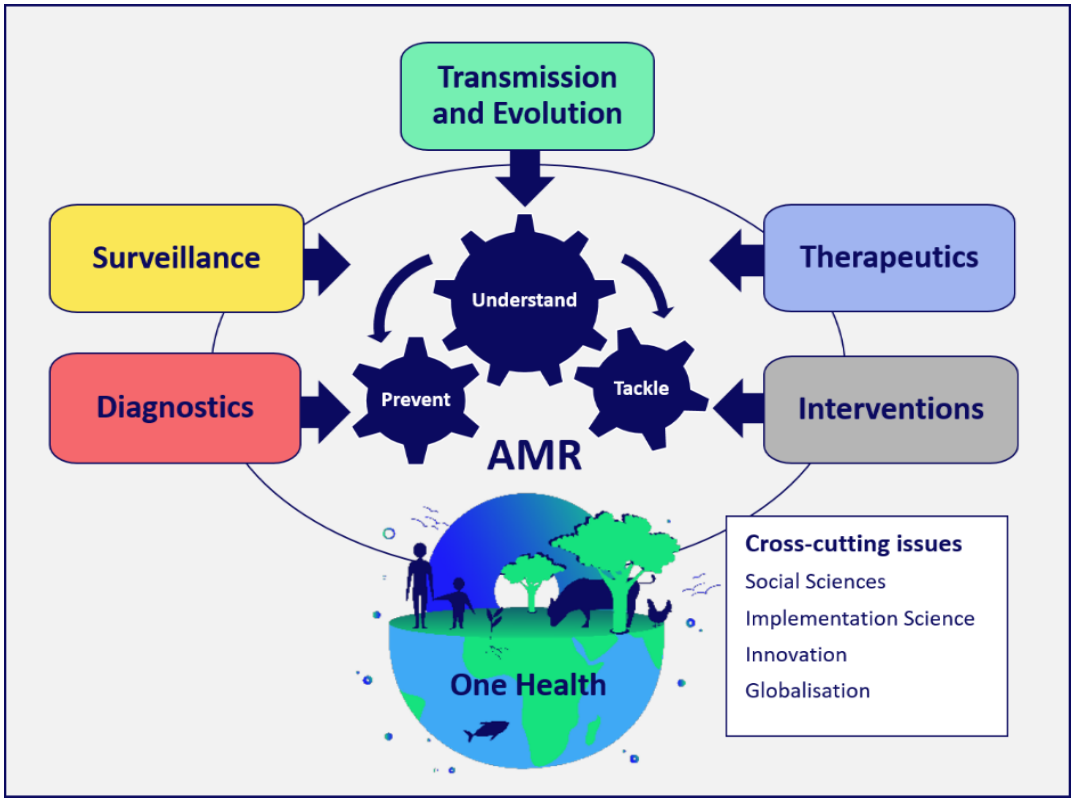


Figure 1. The five thematic areas and the four cross-cutting issues.

One Health approach

One Health is a term used to describe a principle that recognises that human, animal, plant and environmental health are inextricably linked, and that diseases and antimicrobial resistance are transmitted from humans to animals and *vice versa* with increasing realisation of the importance of plants and the environment in development and transmission of AMR. Human activities play a role in the spread of AMR. Antimicrobials used in food animals, (albeit this has been reduced and managed recently in Europe), in companion and sporting animals encourage the selection of drug resistant microorganisms, which can then spread to humans through food consumption, inhalation and through direct contact of humans with animals. Antimicrobials from both human, animal and crop use, as well as the resistant microbes and their genetic material, can also contaminate the environment via wastewater, animal manure, composted crop

materials, dust or insects that populate farms, making the environment a link between humans and animals and a reservoir of AMR. Besides being a threat to human health, AMR complicates the prevention and treatment of infections in animals, which negatively influences animal welfare and can threaten food production.

For this reason, decreasing the tremendous impact of AMR on human health requires a better understanding of the evolution and transmission of resistance between the different One Health sectors as well as solutions to prevent this. Although the requirement to use a One Health Approach is widely accepted by the AMR community, cooperation and multidisciplinary collaboration between different disciplines and groups still represents a major challenge. At the global level, four UN agencies, the Food and Agriculture Organisation of the UN (FAO), the World Health Organization (WHO), the UN Environment Programme (UNEP) and the World Organisation for Animal Health (WOAH, founded as OIE) combined their efforts to establish a global coordinated approach to the problem. At the research level, both the Joint Programming Initiative on antimicrobial resistance (JPIAMR)[17], the One Health European Joint Programme (EJP One Health) [18] and the first Joint Action an antimicrobial resistance (JAMRAI) [19] strengthened the links between different communities and stakeholders, and encouraged an overall One Health approach to curb AMR. The One Health AMR Partnership is expected to both pursue and reinforce this tendency. Within the JPIAMR/ One Health AMR partnership framework, the One Health approach will focus on a better understanding how the use of antimicrobials and the spread of drug resistant microorganisms and resistance determinants in and/or between humans, animals, plants and the environment contribute to the emergence and spread of AMR in humans and to its health consequences, and which interventions are effective in controlling AMR. The research and innovation objectives described in this document aim to integrate the three One Health settings.

[17] JPIAMR (2021), *Strategic Research and Innovation Agenda on Antimicrobial Resistance*
[18] EJP One Health (2019), *Strategic Research Agenda*
[19] JAMRAI Website

Table 2. Examples of the research and innovation priorities in human health, animal health, and environmental health addressed in the different thematic areas.

Thematic Area	Human Health	Animal Health	Environment/Plants
Therapeutics	➢ Identify and develop novel therapeutic solutions for human use and improve the existing ones.	➢ Identify and develop novel therapeutic solutions prioritised for animal use with low risk of cross-resistance to humans. ➢ Provide data to guide policy makers regarding the restriction of some antimicrobials for human use only. ➢ Improve current treatment regimens in animal health in the context of the safeguarded list of antimicrobials for human use only (this objective will be conducted in synergy with the EUP AH&W[20]).	➢ Identify and develop techniques for the disposal and recycling of unused antimicrobials and for decreasing the environmental impact of antimicrobials, including "green chemistry" and biodegradable scaffolds. ➢ Identify ways (both though technical measures and policy changes) to reduce environmental discharges of antimicrobial residues from drug production to safe levels. ➢ Use the environment as a source of new compounds. ➢ Develop novel therapeutic solutions prioritised for agriculture with low cross-resistance to humans. ➢ Provide data to guide policy makers regarding the restriction of some antimicrobials for human use only. ➢ Improve current treatment regimens in agriculture in the context of safeguarded list of antimicrobials for human use only.
Diagnostics	➢ Develop diagnostic tools and methods for detecting/ identifying human infections and for measuring the level of susceptibility to treatments.	➢ Develop diagnostic tools and methods for detecting/ identifying animal infections (this objective will be conducted in synergy with the EUP AH&W).	➢ Develop diagnostic tools and methods for detecting/identifying crop infections. ➢ Develop rapid testing in the food chain between primary production and the consumer.

[20] *EUP AH&W: European Partnership on Animal Health and Welfare. AMR issues specific to food producing animals will be covered in this partnership.*

		➢ Adapt different sampling techniques and protocols to efficiently implement diagnostic use in herds and veterinary hospitals (this objective will be conducted in synergy with the EUP AH&W). ➢ Develop rapid testing in the food chain between primary production and the consumer.	
Surveillance	➢ Optimise surveillance systems in clinical settings to guide antimicrobial prescribing and evaluate the impact of interventions.	➢ Optimise surveillance systems in veterinary medicine to guide antimicrobial prescribing and evaluate the impact of interventions (this objective will be conducted in synergy with the EUP AH&W).	➢ Investigate how environmental surveillance could be used to assess the local regional resistance situation, to reflect antimicrobial use and to estimate risk for AMR transmission via environment and thereby inform policies.
	➢ Improve/develop methods for combined surveillance of human, animal, environment, and food sources.		
Transmission & Evolution	➢ Identify the drivers for the development of resistance, and its transmission within and/or between One Health settings.		
Interventions for prevention & mitigation	➢ Design and evaluate interventions aiming to prevent the need for antimicrobials in the three One Health settings, to promote appropriate use of the antimicrobials in the three One Health settings and to decrease the transmission of resistance between different One Health settings.		

Antiviral and antiparasitic resistance

In 2019, bacterial AMR was the third leading cause of death (only ischaemic heart disease and stroke accounted for more deaths that year)[21]. While fungal infections are less common in healthy people, they are more common in immunocompromised individuals, for example people suffering from HIV, or under immunosuppressive treatments for cancer. Mortality due to fungal infection ranges from 30-90% depending on the pathogen, any associated drug resistance and the patient population[22]. For these reasons antibiotic and antifungal resistance are widely recognised as a major threat to

[21]Murray C.J.L et al. (2022). *Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis;* DOI: 10.1016/S0140-6736(21)02724-0
[22] Fischer M.C. et al. (2020) *Threats Posed by the Fungal Kingdom to Humans, Wildlife, and Agriculture;* DOI: 10.1128/mBio.00449-20

public health[23]. Currently, antiviral resistance has been well documented for HIV while antiparasitic resistance is well documented for malaria, as well as helminthic diseases in animal health. Less data is available to characterise the burden of other antiviral and antiparasitic drug resistance and their impact on human health is currently difficult to assess. However, the high level of use of antiviral and antiparasitic agents, both in human health and in agriculture, associated with an increase in risk of transmission (for example, the extensive geographic distribution of mosquitos due to global warming), is likely to lead to a drastic increase in antiviral and antiparasitic resistance in the coming years. For this reason, the candidate One Health AMR partnership considers that it is timely to address this possible threat, and plan how to overcome this, should it arise. Currently, specific issues related to antiviral and antiparasitic resistance have not been underlined in the research and innovation objectives in this document. However, the intention of the candidate partnership is to propose future actions to raise the awareness of virologists and parasitologists to the issue of drug resistance and to connect the different scientific communities. The lessons learned and the subsequent progress made for antibacterial resistance might benefit virologists and parasitologists. The future partnership will identify the research and innovation questions that researchers would like to address in the coming years on these issues.

[23] CDC; (2019), *Antibiotic Resistance Threats in the United States*; doi: 10.15620/cdc:82532.

Thematic areas

Therapeutics

Discover new therapeutic targets, develop new antimicrobial agents and therapeutic alternatives, and improve existing antimicrobials and treatment regimens.

The goal of this priority area is to improve current antimicrobial therapies by enhancing discovery, preclinical and early clinical development of novel antimicrobial treatment strategies, exploring the repurposing of existing drugs as well as by optimising drug delivery and treatment protocols. An additional aim is to initiate research into the possibilities and effects of minimising barriers for the introduction of novel antimicrobial agents and therapeutic alternatives by proposing innovative regulatory procedures and alternative economic models to stimulate AMR innovation while ensuring a high level of acceptability to end-users, appropriate use through antimicrobial stewardship and minimal impact on the environment.

Introduction

Tackling the rapid emergence and spread of AMR requires continuous development of new antimicrobial agents, and new antimicrobial strategies. The scientific challenge of developing new and innovative antimicrobial agents and the poor return in investment are major factors contributing to the general decline in pharmaceutical R&D of antimicrobial agents. The development and availability of antimicrobial agents for use in the paediatric population and in LMICs are even more limited, and appropriate studies need to be conducted to ensure availability of therapeutic treatments for these specific populations. In the period 2019-2021, only 3 new antibiotics were approved by either the FDA or the EMA. The WHO conducted an annual review of publicly available information[24] 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 published in May 2022, limited to new therapeutic entities in phase 1-3 clinical trials, revealed that a total of 45 antibiotics and/or combinations and 32 non-traditional agents were in the clinical pipeline in 2021, with 27 new therapeutic entities that target priority bacterial pathogens of which only six are considered innovative[30]. A comparison between the report published in 2019[25] and the one from 2022 reveals that in three years, the number of traditional antibiotics and/or combinations in phase 1-3 clinical trials decreased by 10%, underlining, the urgency of the situation. The challenge is even greater for fungi, which are eukaryotes with a relatively high degree of phylogenetic similarity to human cells and therefore offer relatively fewer differential

[24] World Health Organisation. 2022. *Antibacterial agents in clinical and preclinical development: an overview and analysis*. ISBN: 9789240047655

[25] World Health Organisation. 2019. *Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline*. ISBN 978-92-4-000019-3

targets that can be exploited for antifungal drug development. Therapeutic solutions against the fungi included in the WHO priority pathogens list are urgently needed.[26]

Although it is important for academic laboratories to continue their research efforts to identify new therapeutic targets, and new drug leads, increased collaboration with Small and Medium enterprises (SMEs) and pharmaceutical companies is needed to accelerate the transfer from bench to bedside.

With the exception of the ENABLE project[27] (2008-2021), the Innovative Medicines Initiative (IMI), replaced in 2021 by the Innovative Health Initiative (IHI), Novo-REPAIR[28], CARB-X[29], and GARDP[30] provide financial support progressing programs from candidate selection through to clinical development but do not include early discovery. For antifungals, the situation regarding the development of new agents is even more problematic, with few, if any, private partner organisations and funding initiatives committing support to development of new therapeutics. Most recent EU support was devoted to nanocoatings[31] while the funding support to new antifungals is almost non-existent.

Given the challenge of developing new antimicrobials, optimising the use of new and existing agents is required to maximise efficacy and protect against future resistance. Improved dosage, duration of treatment, and combinations of antimicrobials could prevent the development and transmission of AMR. In addition, considering the importance of new antimicrobial agents for human medicine, it is expected that novel antimicrobial agents or classes of agents will, if possible, be safeguarded for human use only and use in veterinary medicine, agriculture or aquaculture will not be permitted. It is therefore essential that current treatment regimens in animal health, including that of companion animals, and protocols for use in agricultural settings are improved using a One Health Approach, and that alternatives to antimicrobials are developed and tested to prevent and combat infections in both animals and agriculture.

Collaboration between different research disciplines is needed to offer innovative therapeutic solutions. For example, the design of novel strategies should include interdisciplinary research within the life sciences community as well as social sciences research. These collaborations should be developed at an early stage to understand the barriers to uptake and how these may be overcome. If COVID-19 demonstrated the benefit of developing alternatives strategies to fight against infectious diseases, the pandemic also revealed the need to improve knowledge around and the acceptance of such strategies by patients as well as clinicians, and other health care professionals. Work will also be needed to address the acceptance of novel strategies by regulatory authorities and by public and private medical insurance systems. Therapeutics will also

[26] World Health Organisation. 2022. *WHO fungal priority pathogens list to guide research, development and public health action*. ISBN 978-92-4-006024-1

[27] *European Gram-negative Antibacterial Engine, IMI Website. https://www.imi.europa.eu/projects-results/project-factsheets/enable*

[28] Novo Holdings established REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund. https://www.repair-impact-fund.com

[29] Combating Antibiotic Resistant Bacteria; https://carb-x.org/

[30] *Global Antibiotic Research and Development Partnership. https://gardp.org/*

[31] *https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-cl4-2021-resilience-01-20*

benefit from the recent advances in personalised medicine, system biology and computational sciences

The search for new antimicrobials should stem from proven unmet medical need, rely on strong science and be transferable to drug developers. In addition, in order to maximise the chances for a new molecule or alternative strategies of reaching the end-users collaboration between clinicians, academics and industry should be facilitated through crosstalk, exchange of views and capacity building amongst the wide innovation ecosystem.

Developing new antimicrobial agents or protocols should not be limited to development of novel therapeutics and clinical trials but should also consider the way molecules or protocols will be accessible to targeted populations, including underserved populations including in LMICs (see also the section on Prevention and Intervention). The accessibility of the drug in local markets, the price of new drugs in comparison of existing drugs, as well as training the local population to the new protocols should be considered in the early phase of the therapeutic pipeline. In addition, the consequences on the environment should also be considered at the first stage of the development. In particular, the drug's ability to be rapidly degraded when released into the environment could be a valuable addition to the development plan for new drugs. The environmental discharge from drug production should also be taken into account and reduced as much as possible.

Research and innovation objectives

1. Identify new antimicrobials, novel alternatives for antimicrobials, and improved delivery methods

Discovery of novel antimicrobial agents is required to fill the gaps in the current therapeutic pipeline. This strategy includes the discovery of novel antimicrobial agent classes that are active against new targets. 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 host-pathogen interactions and could be useful for discovery of new antimicrobial targets. Research aimed at understanding the mechanisms of resistance (see also the section on Transmission and Evolution) can also provide useful information to help identify new antimicrobial targets. In addition to work on new targets, innovative synthetic biology or chemistry strategies could also provide novel chemical scaffolds for antimicrobial agents active on validated targets but capable of overcoming resistance mechanisms. This could include identifying agents which act on the same target but with different modes of action or new interaction sites. In both cases, exploring "green chemistry", biodegradable scaffolds, and enzybiotics, could be beneficial to minimise the environmental discharge of antimicrobial production and use. These approaches could complement the more traditional screening of chemical libraries (including natural compounds) and the structure guide design of new molecules.

Once the compound candidate is identified, research is needed to improve the physicochemical and pharmacological properties of the lead compound while reducing its toxicity (including its effect on the host microbiota), as well as its propensity to select for resistance. When developing new antimicrobials for veterinary medicine and agricultural sectors, the likelihood of cross-resistance to antimicrobials for human medical use should be carefully evaluated. Exploring mechanisms of resistance to candidate drugs in different species and environments could guide drug development/modification in a direction to reduce risks for rapid horizontal acquisition of resistance after market introduction. A guidance for such evaluation needs to be developed which includes wildlife bacterial and fungal diseases and a comprehensive One Health approach. New methodologies that can help optimise the physicochemical properties of antimicrobial agents should be encouraged, including approaches that can inform the ability of such agents to enter Gram-negative bacteria.

Research should also propose new strategies to improve the delivery of new compounds based on traditional and novel technologies, including nanotechnologies. Delivery methods should be explored at early stages of antimicrobial discovery and development (i.e., prior to the clinical trial phase). For example, the development of alternative delivery methods such as inhaled antibiotics could improve drug targeting and be more acceptable to patients.

Alternatives to antimicrobials could also be useful to replace or complement the activity of traditional antimicrobial agents. Their development should be pursued, aiming to improving the efficacy of treatments and overcoming and reducing selection of resistance and adverse effects associated with their use (including impacts on the microbiome). Specific alternatives could address, for example (i) anti-virulence strategies, (ii) bacteriophages, endolysins and fungal viruses, (iii) antimicrobial peptides and peptidomimetics, anti-biofilm agents, agents preventing sporulation (fungi) or host defence peptides. A further promising approach is the modulation of the human microbiota that has been explored to treat infections by *Clostridiodes difficile,* and could have additional preventive or therapeutic applications. Studies aiming to understand the barriers (including the social individual and societal acceptance of alternative strategies, and organisational constraints) to uptake of alternative strategies and how these may be overcome would be required.

New antimicrobials and alternatives for antimicrobials, would also be useful for companion animals since veterinarians have to manage infections caused by the multidrug-resistant pathogens using a very limited antibiotic arsenal. However, new antimicrobials and treatment protocols for veterinary use should meet the basic requirement that they are not usable in human medicine, for example for reasons related to toxicity or poor pharmacokinetics in humans. When developing new antimicrobials for non-human use, the risk of cross-resistance to antimicrobials for human medical use should be carefully evaluated using a comprehensive One Health approach.

2. Unlock the unexplored potential of existing and neglected antimicrobials by improving PK/PD and enabling repurposing and combination therapies

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 of existing drugs to treat infections. Appropriate routes of administration should focus on maximising delivery of the drug at the site of infection. In addition, to shorten the time of treatment and to decrease potential side effects, appropriate PK-PD research studying combinations of existing drugs and new ones, and the development of pathogen-specific combinations is required. PK-PD varies between patients and is related to demographic groupings and pathophysiological profiles. Inter differences in PK-PD can result in adverse reactions due to toxicity, as well as suboptimal drug concentrations at the infection site that impact the outcome and can induce development of drug resistance. In the light of personalised medicine, approaches tailoring antimicrobial selection and dosing to specific patient categories, studies of PK-PD should be extended to patient groups not covered in registration trials (e.g., obese patients, neonates, children, patients with cystic fibrosis, transplanted patients, patients with extracorporeal circuits, and patients suffering from malnutrition).

The role of novel and innovative combinations of compounds (using known antimicrobial agents, or existing antimicrobials in combination with new antimicrobial, repurposed drugs, or new antimicrobial strategies) should be investigated especially for multidrug resistance and co-infections. Research focused on combination treatments should address differences in pharmacology of the combined agents as well as potential adverse interactions, impacts 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 have 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), and is standard practice for the treatment of fungal (cryptococcal) meningitis. Nevertheless, combination therapy to prevent resistance is still underused and under-researched for treatment of bacterial and fungal infections. There is a need for a coordinated approach between the pharmaceutical industry and academia to support exploration and development of combination treatments using both traditional and novel 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.

Considering that a list of antimicrobials is likely to be safeguarded for human use only and use in veterinary medicine, agriculture or aquaculture will not be permitted, improving current treatment regimens in animal health and protocols for use of antimicrobials in agricultural settings will be critical (objective to be explored in collaboration with the partnership animal health and welfare). For antimicrobials that are already authorized for veterinary and agricultural use, research is required to assess

the impact of different drugs, formulations, routes of administration and treatment regimens on the risk of emergence of AMR and potential further AMR transmission to humans and the environment, and to inform the policies related to the restriction of some antimicrobials for human use only (see also the Transmission and evolution section).

3. Develop methods to facilitate the approval and registration of new antimicrobial agents or novel therapeutic strategies

The discovery of a novel antimicrobial agent or of a novel therapeutic strategy does not guarantee successful implementation in clinics or for veterinary use. Research is required at each step of the process to maximise successful translation of cutting-edge early-stage research into clinical practice.

Most new compounds or novel antimicrobial strategies fail during clinical trials. Research should propose new approaches to streamline and de-risk both preclinical development and early phase clinical studies in order to maximise the probability of a new drug ultimately succeeding and reaching the clinic and shorten the time for this to occur within an acceptable ethical framework. Research could, for example, support the development a wide range of preclinical models, recapitulating specific or multiple pathophysiological disease states, for screening the effectiveness and toxicity of candidate drugs, predicting the likelihood of development of drug resistance and predicting success in the clinics. Research could also propose methods to facilitate patient recruitment during clinical trials or to decrease cost, especially in the absence of an associated rapid diagnostic test, where there are a limited number of patients impacted by a pathogen, or where patients present complex clinical situations (particularly frequent for patients affected by fungal infections).

Current regulation might also slow down or impede the transfer of novel solutions to end-users. For example, the development of alternative strategies might be jeopardised by the lack of proper tools and guidance to evaluate their true potential and specificity. Available guidelines solely rely on the gold standard Minimum Inhibitory Concentration (MIC)-Probability of target attainment (PTA) methods to evaluate drug candidates' efficacy. Unfortunately, these methods are solely relevant to evaluate activity on fast-growing pathogens. A significant number of products under development cannot be evaluated by MIC, as they do not only inhibit the growth of pathogens (direct killing for example). Joint effort (research, industry, medical community, regulatory bodies) is needed to identify complementary efficacy end-points e.g., activity against tolerant behaviours or measurement of time-to-cure, especially when a discrepancy is observed between the MIC-PTA data and the clinical data. These new endpoints would allow comparison of compounds beyond their MICs, providing a scientific rationale (basis) to select a treatment when these properties are important (e.g activity against biofilm) and increasing the differentiation margin of the compounds in development. Research focused on ethics should provide guidance for the policy makers to aid in defining a proper balance between the environmental cost associated with the use of some antimicrobials (and possible indirect human cost in the future years), and the direct human cost associated with the possible immediate death of the patients in absence of

efficient treatments. Finally, research should also support the pharmaceutical industry in complying with national and international regulations by proposing new industrial methods aimed at reducing contamination of the environment with resistant bacteria, fungi and antimicrobial residues at the production site (see also the Prevention and Intervention section).

Once approved by regulatory authorities, careful targeting of antimicrobial agents could optimise their safety and cost effectiveness. Rapid diagnostics, including point of care diagnostics, are essential for optimal choice of antimicrobials (see also the section on Diagnostics). Innovative tools applying artificial intelligence (machine-learning application for risk definition, decision support systems for personalised therapies) need to be explored. Research should also support post-approval studies and help to build evidence for product use across relevant indications, for specific and underserved populations and for specific pathogens.

The approval of new antimicrobial agents, new treatment protocols, and new antimicrobial strategies by the public authorities does not guarantee their uptake by end-users. Research should show how the current national regulations (or absence of regulations) and national and regional public and private organisations (in particular the economic weight of some local pharmaceutical producers, and the access to a structured health care system) could influence their uptake. Research should propose novel strategies (at an individual level, or at a systemic level) to improve the uptake of innovative treatment solutions (see also the Prevention and Intervention section).

4. Develop strategies to minimise the structural and economic barriers to research, development, availability of and access to new therapies and alternative therapeutic strategies

The current pipeline of new antimicrobials is fragile, mainly as a consequence of scientific challenges and a broken market which discourages investment from the private sector thus creating severe obstacles to the translation of fundamental discoveries into antimicrobial drug discovery programmes. On the other hand, antimicrobial therapeutics as a common good need to be protected through structural changes aimed to ensuring their sustainable development, availability, access and appropriate use.

To fix the broken antimicrobial market and unlock the innovation potential in antimicrobial R&D, fundamental economic research has proposed new models such as the delinking of revenues from the volume of sales to guarantee a fair and predictable revenue for the drug developer while maintaining strict stewardship policy standards. Such incentives should only be made available to those therapeutics that demonstrate clinical utility (the boundaries of clinical utility still need to be precisely defined). Further economic research needs to help design the required international framework under which each country could provide fair economic contributions to solve the problem. To achieve this goal, economic research needs to develop quantitative models so that policy makers understand the relationship between guaranteed revenues for the drug developer and availability of innovative antimicrobials. Economists should also design rules for the contribution of each country to finance the innovator's revenue: for

example, should contributions depend on the population size of each country or gross domestic production, total health expenditures or on the need for the new therapeutic solution being developed (objective to be explored in collaboration with the Joint Action 2 on antimicrobial resistance and HERA, the Health Emergency Preparedness and Response Authority).

The development of new economic policies should also guarantee the availability of new and old drugs in LMICs. Engagement with local LMIC stakeholders should be sought to optimise widespread access, distribution and implementation.

Research should be carried out to better understand the socio-economic challenges associated with the production, distribution and access to novel antimicrobials by studying the roles of key stakeholders (e.g., institutional, commercial, legal, ethical, end-users) across the value chain. Research in social sciences should also identify existing and unanticipated drivers behind the misuse of antimicrobials and the emergence of resistance. Such drivers could be of an individual nature (cognitive and socio-psychological) or structural (e.g., through existing healthcare or industrial schemes and infrastructures that encourage misuse or overuse of antimicrobials). Research proposing solutions to better control drug quality, pollution from drug manufacturing, marketing/sales and use, paying specific attention to generic production, unlicensed internet sales and black market that facilitates the use of poor-quality drugs (falsified, substandard, or degraded) in different national contexts is needed. In addition, techniques encouraging the disposal and recycling of unused antimicrobials in different local contexts should also be promoted (see also the Prevention and Intervention chapter).

Diagnostics

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

The goal of this priority area is to stimulate the design, development, evaluation and implementation of diagnostics to ensure appropriate use of antimicrobials in the treatment of bacterial and fungal infections. Appropriate diagnostic tools can also be used to support interventions to tackle AMR, including infection prevention and control, and antimicrobial stewardship. In infectious diseases, diagnostics are most commonly used to identify which pathogen(s) are causing symptoms. Diagnostics are typically used to identify a disease or its cause and are considered in all three One Health settings, including the emerging topic of environmental diagnostics. Of particular interest are infections caused by antimicrobial-resistant pathogens of clinical importance. Tests allowing rapid detection of drug susceptibility are required to support rational clinical decision-making and stewardship, leading to a more targeted and sustainable use of antimicrobials in all One Health settings.

Introduction

A diagnostic test is used to provide information about a disease in order to prevent or treat it. A radical change in the way antibiotics and antifungals are used is necessary since antibiotics and antifungals may be prescribed and used incorrectly, i.e., in the absence of a bacterial or fungal infection, or against a pathogen that is resistant to the prescribed antimicrobial drug. This incorrect use most often results from physicians, veterinarians and other antimicrobial prescribers being unable to make a precise diagnosis of an infection in real-time, and resorting to empirical treatment. Rapid and affordable diagnostics should be developed and made accessible for use for detection of bacterial and fungal infections as well as antimicrobial susceptibility testing. This will prevent physicians and veterinarians from prescribing antimicrobials empirically when they suspect an infection. Diagnosis of fungal infection and fungal drug resistance is particularly problematic. Only few, if any, diagnostics are available to aid the appropriate prescription of antifungals for use in clinical and agricultural settings.

The overall volume of antibacterial and antifungal drug use is positively associated with drug resistance. Therefore, the control of the demand for antimicrobials and reduction of their use through development and use of rapid and cost-effective diagnostics to detect bacterial and fungal infections and antimicrobial susceptibility would reduce the selection pressure for AMR. 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 species identification and antimicrobial susceptibility testing. Special attention should be directed towards the development of diagnostics that can be used for detection of infections and AMR in specific groups, such as paediatric patients. The implementation of rapid diagnostics for

bacterial and fungal infections and antimicrobial susceptibility also requires major behavioural changes by clinicians, veterinarians, and patients. Ideally, the result of a rapid test should be available to prescribers before any antimicrobial drug can be prescribed and used. The positive effect of the wide-scale introduction of rapid diagnostics on minimising the emergence and spread of AMR is predicted. However, to date, there is insufficient evidence in support of this theory. The success of novel diagnostics will 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 in resource-constrained settings. The cost of a diagnostic tool is particularly important in the veterinary and agricultural sector due to the societal demand to produce food at low cost, the lack of reimbursement mechanisms and incentives in agriculture, and the limited diffusion of insurance policies that cover diagnostic costs for companion animals.

Drug and diagnostic co-development and use 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. Diagnostics accompanying the development and/or approval of new antimicrobials would be a promising approach to delay the development of resistance to these compounds and to enable their use within the scope of personalised medicine (see also the Therapeutics section).

Rapid and reasonably priced tests to guide antimicrobial prescription by veterinarians are urgently needed since the range of therapeutic options that are available for animals are very limited due to restrictions on veterinary use of antimicrobials critically important for human use, combined with the historical lack of development of new veterinary drugs. Innovative approaches based on artificial intelligence are required in order to identify new diagnostic or prognostic markers and for developing early warning systems that allow detection of humans or animals predisposed to infection. Technologically, the tools for veterinary applications will likely not differ significantly from those used in human medicine. However, different sampling techniques and protocols may be necessary to efficiently implement their use in herds and veterinary hospitals. The use of rapid testing in the food chain between primary production and the consumer would also rapidly identify food products contaminated with drug-resistant organisms, thereby increasing food safety. Diagnostics in environmental settings (test of how much resistant bacteria a sample of environmental media, such as water, contains) could be carried out to inform specific, local measures to reduce risks for e.g., transmission. Diagnostic are also used for crop infections caused by bacterial or fungal pathogens.

Novel technologies have already been developed to identify microbial pathogens and AMR, and if used effectively, many of these technologies could optimise antimicrobial prescription and use. Although implementation of these new technologies has the potential to improve infection outcomes, they typically increase costs of care since innovators often focus more on the performance and costs achieved rather than on the greater outcome delivered. This occurs particularly since many diagnostics have not

been developed with the reality of One Health in mind, including current clinical practices, primary care and hospital infrastructure, animal management practices, etc. 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 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 applications are needed.

The successful introduction of early diagnostics is dependent on the awareness and empowerment of patients and other stakeholders. These stakeholders should be provided with appropriate information as it has been shown that strategies to improve health literacy and AMR awareness often result in changes in medicine consumption. Health-literate patients have better health outcomes and an increase quality of life, improved awareness and knowledge regarding medicine use, and these individuals often 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 veterinary and agricultural sectors, educational efforts should be aimed at farmers and companion animal owners who need to understand the benefits of rapid testing to guide appropriate treatment. Finally, significant differences exist between the needs of the HIC and LMICs, and strategies regarding the use of diagnostics will likely differ in different cultural and socio-economic settings.

The development of rapid diagnostics requires secure funding for periods long enough to ensure their development from concept to production and assure implementation, both in HIC and in LMICs. 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 end-users and to bring together disparate technologies into simple, integrated systems at a reasonable cost.

A regional or global platform to evaluate rapid diagnostics by aligning payers and providers, as well as engaging those who use and benefit from these diagnostics 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 other regions, should be made available for the development of these diagnostics. The selection of appropriate targets for detection and identification of pathogens and their resistance characteristics is critical.

Research and innovation objectives

1. Discover, design and evaluate new diagnostics and improve the efficacy of existing ones

Development of novel diagnostics and improvement of existing tools must be driven by needs in settings where the risk of antimicrobial misuse and/or overuse is higher or where there is a substantial risk of treatment failure due to AMR. Ultimately, new diagnostics should be affordable, rapid and suitable for use in LMICs and ideally at the point-of-care or point-of-need. Novel diagnostics could consider the appropriate user requirement and functional requirement specifications defined by the respective intended use, leading to shorter time to results through rapid diagnostics and more cost-effective solutions.

Novel diagnostic markers and tests that accurately identify infections requiring antimicrobial therapy and distinguish between bacterial, fungal, parasitic and viral infections are critical for aiding antimicrobial prescribing practices, and stewardship. Diagnostics should be further expanded to quickly evaluate the susceptibility of the target pathogen to antimicrobials. New diagnostics should be unaffected by or able to discriminate between colonising or contaminating organisms and those causing infection. The development of innovative prognostic tests should be considered whenever such tests can be used in efforts to predict and ideally prevent disease, and thereby reduce antimicrobial use.

In companion animal veterinary medicine, new diagnostics should meet the societal demand to minimise and rationalise antimicrobial use and are particularly needed to guide antimicrobial treatment of common infections associated with multidrug-resistant bacteria. Research is also needed for setting and validating host-, bacterial species- and disease-specific interpretive criteria for antimicrobial susceptibility testing of important veterinary bacterial and fungal pathogens for which such criteria are lacking or have not been validated clinically. Diagnostics in livestock and aquaculture targeting food producing animals will be largely covered by the European Partnership for Animal Health and Welfare (EUP AH&W). The OHAMR will be in close contact with EUP AH&W to maximise the synergy of the programmes and ensure that the challenge of AMR is addressed using a One Health perspective.

Validated and standardised diagnostic methods for selection and quantitative assessment of the efficacy of unconventional antimicrobials (e.g., phage or virulence inhibitors) and alternatives to antimicrobials (e.g., prebiotics and probiotics) or other interventions would be useful to facilitate the use of these products in clinical practice across any sectors, thereby reducing antimicrobial use and AMR selective pressure. Further, diagnostics play a vital role in supporting other, non-therapeutic interventions such as infection prevention and control (IPC) in hospitals and water, sanitation and hygiene (WASH) in communities e.g., through testing of patients for MRSA or ESBL/CPE carriage (see also the section on Preventive and Mitigating Interventions).

New diagnostic developments should be evaluated using the specimen and target analytes they are intended for. Accordingly, these studies should provide information

on the analytical sensitivity and specificity. For the development and validation of novel diagnostic platforms, it is essential to use standardised materials for testing. To this aim, accessible biobanks for industry and academia are needed. Such biobanks should include collections of several thousands of microbial strains and purified genomic DNA, sequences of genes, genomes and metagenomes, panels for quality control testing and well-characterised clinical samples with relevant clinical information. In turn, such platforms should be exploited using innovative approaches based on artificial intelligence to identify new diagnostic or prognostic markers and developing early warning systems that allow detection of human or animal individuals predisposed to infection.

Depending on the intended use, new rapid diagnostic platforms should allow data connectivity, analysis and reporting by wireless communication using secure protocols and existing cellular networks. Ideally, the results should be accessible and interpretable by mobile devices, and easily exchangeable with local, national and global surveillance systems to improve epidemiological surveillance of AMR and guide targeted interventions to optimise antimicrobial use (see also the Surveillance section).

2. Evaluate field performance, feasibility and impact of diagnostics

Well-designed pre-clinical studies and clinical trials as well as agricultural and environmental studies, need to be conducted to evaluate field performance, feasibility and impact of innovative diagnostics. Optimal integration and implementation of these diagnostics into human, animal and plant healthcare practice, should be evaluated and their impact on healthcare systems should be thoroughly assessed. One expected outcome is to be able to define the diagnostic performance, including clinical sensitivity, specificity and positive and negative predictive values. The evaluation outcomes will contribute to improve diagnostic tools. Research is required to understand how robust diagnostic methods are. This will be an important parameter when deploying the diagnostic tools to the intended users.

Once new diagnostics have been developed and their validity (improved outcomes) has been demonstrated, utility (improved decision-making by antimicrobial prescribers and improved access), applicability and cost-effectiveness need to be studied in the relevant One Health setting. Studies to evaluate and provide evidence for the benefit of using diagnostics are required. These should consider any impact on health economics, integration with antimicrobial stewardship, antimicrobial prescription, clinical outcomes, burden of AMR, AMR prevalence, and other societal factors. To do this, these studies require appropriate health economic models, tools to quantify impact and enhanced understanding on factors influencing AMR prevalence, including how reduced antibiotic consumption impacts AMR prevalence. 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 how the novel methods can be integrated in current diagnostic flows and adapted to healthcare. Cost-effectiveness studies are specifically needed for fungal diagnostics, as in contrast with antibiotics, treatment of

fungal infections is comparatively expensive, and the use of rapid diagnostics could have an economic benefit.

3. Identify and overcome barriers for implementation and acceptance of diagnostics

Since available antifungal susceptibility tests are rarely adopted or not routinely performed, an effort should be made to understand specific barriers for implementation of antifungal susceptibility testing and develop strategies for overcoming such barriers in relevant One Health settings. Barriers and facilitators to the acceptance and uptake of new diagnostics should be identified using an interdisciplinary approach. Identification of such barriers is beneficial to understand behavioural, cultural, infrastructural (e.g., availability of trained staff and appropriate equipment) and economic factors (including reimbursement and incentive systems, regulatory frameworks, and economic limitations and restrictions) that may be changed to improve implementation and acceptance of new diagnostics by the relevant end users, including healthcare professionals and patients or companion animal owners as well as farmers and agronomists. The influence of public perception of diagnostics should be considered in relation to the adoption and continued use of diagnostics, especially in view of the experiences during the COVID-19 pandemic.

Surveillance

Optimise surveillance systems to understand the drivers and burden of antimicrobial resistance in a One Health perspective and support decision making at all levels.

The goal of this priority area is to strengthen the research on surveillance systems, methods, interpretative guidelines, and communication tools to optimise the surveillance of AMR and antimicrobial use and consumption (AMU/AMC) using a One Health approach, in order to inform the prevention and treatment of infections in humans, animals and crops. Surveillance may also serve as an indicator to assess the impact of interventions to mitigate AMR and inappropriate AMU in humans, animals, crops and the environment.

Introduction

Surveillance is the continuous, systematic collection, analysis, interpretation and collection of data needed for action, e.g., to inform effective empirical treatment with antimicrobials, and the planning, implementation, and evaluation of interventions to mitigate AMR and its societal and economic impact. AMR surveillance is needed for One Health policy purposes to understand the development, transmission, directionality and risk of the spread of AMR and to estimate the nature and burden of AMR in global and local settings. Surveillance data informs decision making on AMR and AMU/AMC by any stakeholder in the different One Health sectors. Surveillance in the environment and in food systems may serve as an early warning system that could in turn strengthen the response to the emergence or escalation of AMR and inappropriate AMU/AMC and the outbreak of drug-resistant bacteria and fungi in human and animal health. Surveillance systems/frameworks should thus be fit for purpose.

A standardised and harmonised One Health AMR and AMU/AMC surveillance approach to the collection, analysis, interpretation, communication and sharing of data adopted by all countries and complemented by protocols harmonised between sectors, would generate comparable data to mitigate AMR locally, nationally, regionally and globally. In addition, monitoring AMU would encourage countries to adopt regulations to control AMU/AMC in humans, animals, and crops and their disposal in the environment. To be applicable in the medium term and at global scale, a One Health AMR and AMU/AMC surveillance framework must be achievable within available resources.

Research and innovation objectives

1. Optimise, standardise, and harmonise AMR & antimicrobial use/antimicrobial consumption surveillance protocols to achieve or improve cross-compatibility of surveillance systems

The needs of different stakeholders and the contextual and socio-economic situation influencing AMR and AMU/AMC must be explored to ensure that surveillance systems

show fitness of purpose and for purpose locally and globally, considering public health priorities. Surveillance systems should generate accurate, quality-assured integrated and triangulated data in real-time on online/open access formats, for stakeholder action. Research should contribute to improving the standardisation and harmonisation of sampling, analysis and interpretation protocols and workflows to allow the comparison data from different One Health sectors at national, regional and global levels. For example, protocols may be standardised at laboratory level and harmonised between and within different sectors by cross-compatible methods such as establishing tailored sampling schemes for different sectors which collate metadata from different fields. Prioritisation of bacterial and fungal species, prioritisation of antimicrobials (e.g., antibiotics, antifungals, biocides and heavy metals), metrics for AMR (e.g., clinical Breakpoints -CBPs-, epidemiological cut-off values -ECOFFs-, phenotype-genotype correlation, integrated omics) and AMU/AMC are needed in all sectors. Other indicators and metrics (e.g., antibiotic residues in the environment), and estimation and prediction models for AMR and AMU/AMC also deserve special attention.

Specific objectives for research and innovation are to define the components of an integrated and interlinked One Health surveillance system/framework. This should include a minimum sampling framework (sample size, sampling frequency, and standard operating procedures), quality-controlled laboratory investigations and integrated and triangulated analysis, interpretation and communication of AMR and AMU/AMC data. Development CBPs and ECOFF for bacteria and fungi is integral to this. Alignment of and access to surveillance data and platforms between HICs and LMICs and within public and private sectors should be addressed. A minimum, resource-efficient phenotypic and genomic surveillance framework and a platform including whole genome sequencing (WGS) and metagenomics in relation to phenotypic data should be explored.

2. Identify reservoirs and transmission pathways of AMR in and between humans, animals and the environment to enable risk assessment and guide preventative actions

The role of different reservoirs of AMR in humans, animals, crops and the environment in the emergence and spread of AMR resistance need to be better understood for risk assessment and directing interventions. The relative contribution of selective pressures and transmission pathways in different settings also need to be explored. It is important to identify sensible control points (hotspots) and selective pressures (e.g., type, mixtures and concentrations of antimicrobials and other pollutants for selection and co-selection of AMR determinants) to build resource-efficient surveillance systems.

Research is needed on AMR surveillance at interfaces between One Health sectors to generate data to illustrate transmission dynamics for risk assessment and management (see also the Transmission & Evolution Chapter). To this end, agricultural and environmental surveillance protocols for antibiotic and antifungals residues and drug-resistant bacteria and fungi, antimicrobial resistance genes (ARGs) and their associated mobile genetic elements (MGEs) in all sectors should be developed. Critical control points (i.e., hospital and municipal sewage, water systems, food and agricultural waste) should be identified to provide data on antibiotic and antifungal use in humans, animals

and farming systems and provide information on the selection and transmission risks of AMR bacteria and fungi in and via the environment. Novel and rapid technologies that allow accurate determination of abundance and diversity of drug-resistant bacteria and fungi, ARGs and, associated MGEs should be further developed. Methods and metrics for assessing the occurrence and dynamics of AMR at different interfaces need to be developed. Indicators and metrics of operational units of surveillance (quantifiable subjects under scrutiny such as AMR, AMC/AMU, and/or hospital-acquired infections or equivalents) that elucidate the dynamics of AMR, in relation to changes, e.g., in climate, social activities and supply chains should be identified and explored in all sectors. Further research is required to explore if and how metagenomics can be efficiently utilised for rapid detection of drug-resistant pathogens, ARGs and MGEs and to monitor the global spread of AMR more holistically.

Structured surveys and surveillance of the environmental dimensions of AMR should be harmonised by coherent sampling frames and a comparable data structure (methods, metrics, interpretation guidelines, and tailored communication).

3. Optimise the use of surveillance data to estimate the burden of resistance, assess the impact of interventions and enable policy and practice action

Increased understanding and better estimations of the real burden (in terms of infection, animal productivity, mortality, cost etc.) associated with AMR worldwide is needed, especially in LMICs where there is a large knowledge gap and where the AMR burden is disproportionally high. These issues need to be addressed with an interdisciplinary approach that also takes into account cultural and behavioural aspects. Efforts are required to design surveillance databases and analysis, interpretation and communication tools and workflows, especially in LMICs, to assess the impact of One Health interventions on AMR and AMU/AMC reduction, transmission and the overall burden as appropriate. Research should propose methods and tools to link harmonised microbiological information to clinical and epidemiological and social data (e.g., information gathered for diagnostic purposes), patient outcomes and characteristics, and to similar data from the animal, agricultural and environmental sectors. The design of online, real-time and automated analysis could also facilitate the use of surveillance data by optimising its availability. Here, innovation and methodological development may need to include expertise in digitalisation, machine learning, information technology (big data, artificial intelligence, modelling) and similar fields. The utility of environmental surveillance as a resource efficient complement to assess the regional resistance burden, similar to current sewage monitoring for Sars-CoV-2 and polio, should be further explored.

Research should identify which could be the best methods to disseminate scientific evidence in order to create political and public awareness of the importance of managing and limiting the spread of AMR and optimising AMU/AMC in all One Health sectors (for example, by using stakeholder-tailored mass communication tools such as digital social networks). Interactive, updated and user-friendly websites, and mobile applications giving rapid access to AMR and AMU/AMC surveillance data could for example provide access to information to human, animal and environmental health

professionals to support decision-making. Research in social sciences should provide solutions to facilitate the use of these tools, to explore their acceptability in different populations, and to measure their effectiveness.

4. Develop strategies and methods to promote the exchange, interpretation and communication of surveillance data

Research infrastructures should be established or further developed in a coordinated manner to facilitate the integration of surveillance data to perform meta-data analysis at national, regional and global levels. Research should contribute to designing open access data warehouses where integrated surveillance data (AMR phenotypic, genomic and metagenomic data, AMU/AMC, hospital-associated infections (HAIs), clinical and/or environmental indicators) can be imported, and, quality checked, for further action. Additionally, research should propose methods to favour the collection of data on individual isolates into a global repository (for instance by improving bioinformatics pipelines) to allow comparative analyses across geographies, sectors, pathogens and time and to create alerts. The difficulties of implementing open access tools for data sharing due to infrastructure capacity limitations and/or laws/regulations and intellectual property constraints in different countries should be considered.

New technology for AMR surveillance and the design of research infrastructure require capacity building and hands-on, practical training on the generation, analysis, interpretation and communication of AMR and AMU/AMC data, to facilitate the use of surveillance data for action by different stakeholders.

Transmission & Evolution

Understand and prevent the transmission and evolution of antimicrobial resistance in a One Health Context

Over time microorganisms may accumulate antimicrobial resistance determinants by horizontal acquisition of genes, by mutations in pre-existing DNA, and by epigenetic phenomena. Understanding the mechanisms involved and identifying the underlying drivers and conditions that favour such evolution are necessary in order to identify the most efficient ways to prevent or delay the emergence of new, successful, disease-causing resistant strains. A parallel and intertwined process is the transmission of resistant strains, facilitated by or independent of changes in the genetic repertoire of the microorganisms. Exposure to selective agents, including antimicrobials, may boost both transmission of the microorganisms and their evolution. Alternatives to reducing the exposure to antimicrobials and other co-selective agents, such as improved hygiene and sanitation, may be even more critical countermeasures in many situations. A One Health approach that considers the evolution and transmission of microorganisms and their antimicrobial resistance determinants, within and between humans, animals and the environment, is needed to fully address the complexity of the challenge. This approach also covers research in the broader social sciences domain, to understand ultimate drivers and to help design effective interventions adapted to different settings and geographical variations.

Introduction

The dynamics of the evolution and transmission of antimicrobial resistant commensals, pathobionts, and pathogenic microorganisms are complex. Despite a vast diversity of horizontally transferred resistance genes found in clinically important bacteria, our understanding of their more recent origins is limited. The environmental niches, the relative roles of different drivers, and the genetic processes involved in emergence and establishment of antimicrobial resistance in commensals, pathobionts, and pathogens are still largely unknown. Chromosomal bacterial genes with very limited mobility can become mobile through e.g., the association with different mobile elements, such as insertion sequences, integrons, transposons and plasmids. This, in turn, greatly facilitates their spread across strains and species, for example through conjugation. However, in some cases, genetic material is transferred horizontally without prior association with mobile elements, e.g., during transformation. Antifungal resistance is, in contrast, not associated with horizontally mobile genes. Notably, external environments play an important role in selection of antifungal resistance, but the environmental component is less well studied than in antibiotic resistance. Horizontal acquisition of resistance factors as well as resistance causing mutations in existing DNA drive AMR evolution via adaptive processes. These include, for example, mutations that rapidly compensate for fitness costs inferred initially when a microorganism becomes resistant to an antimicrobial. While the emergence and establishment of new, highly

successful, resistant genotypes in human or animal populations are relatively rare events, the consequences of even single events may be vast and global.

For many microorganisms, transmission of resistant strains between individuals (humans or animals), occurs frequently, resulting in colonisation and/or infection. Transmission can be direct or indirect, it can involve the built environment (e.g., surfaces in homes and hospitals) or the wider external environment (e.g., water, soil, dust, produce etc). In some cases, the pathogens' natural life cycle involves the external environment (e.g., *Legionella, Aspergillus, Cryptococcus*), sometimes associated with specific environmental hosts (*Vibrio*). In yet other cases, domestic animals and wildlife serve as critically important reservoirs for zoonotic pathogens (e.g., *Campylobacter, Salmonella*). The intestinal microbiota of humans and animals often function as a reservoir of resistant enteric bacteria. Their release into the environment provides opportunities for the dissemination and exposure of people and animals, especially when water quality, sanitation and hygiene conditions are poor. Resistant bacteria may also spread through trade networks or via the food chain. Dissemination of resistant bacterial strains occurs through transmission between individuals within the community, within and between hospital wards, between community and healthcare institutions, and between different countries. There is also a transfer of resistant bacteria between food animals and humans, through contaminated food and sometimes via the farmer's direct contact with the animals. Some fungal pathogens, such as *Candida auris*, are transmitted between individuals both in hospitals and community settings. However, fungal mould and dimorphic pathogens are often airborne and have a ubiquitous presence in the environment, leading to exposure. Transmission is greatly influenced by behavioural, cultural and socio-economic aspects, for example handwashing habits, migration and tourism, companion animals, agricultural practices (e.g., the use of antimicrobials in crop and food animal production), education, public health and other infrastructures, and trade. Measures that limit transmission of non-resistant microorganisms are generally also effective in limiting the transmission of the resistant counterparts. Still, the amplification of resistant microorganisms through selection by antimicrobials in both "donors" and "recipients" can strongly boost transmission opportunities. What type of contacts that are likely to lead to effective transmission and which ones are not is often still a major knowledge gap.

While antimicrobials are recognised drivers of both evolution and the transmission of resistant bacteria and fungi, there are still major knowledge gaps with regards to e.g., minimal selective concentrations, the role of mixtures or sequential exposures, bioavailability in different matrices as well as co-selection and adaptation in different environments. The coexistence and competition with other microorganisms in e.g., the human, animal or environmental microbiota may have a profound role in modulating the selection by antimicrobials and/or preventing colonisation or infection. Certain biocides and metals (e.g., Zn, Cu, Hg, Ag) also have a potential to co-select for antibiotic resistance through cross- or co-resistance mechanisms. While selection pressures often are strong in the microbiota of humans and domestic animals, there is also widespread contamination of antimicrobials in the external environment, including water and soil. Depending on the environment and the pollution source, concentrations in external

environments span from well above minimal inhibitory concentrations down to non-detectable. Many selective agents may also directly trigger horizontal gene transfer in bacteria, although horizontal gene transfer appears to be driven by a very wide set of (natural and anthropogenic) stressors. The environmental release of faecal matter may also facilitate gene acquisition from the vast environmental gene pool, utilising efficient "capture" elements (integrons, plasmids etc) already well adapted to the human/animal microbiome, as well as providing nutrients needed for cell division.

This research priority aims to improve our understanding of the complexity of how resistance develops and spreads to/within pathobionts and pathogens, and to identify critical control points at which targeted interventions have the potential to substantially limit the consequences of AMR. Multidisciplinary research efforts, including for example clinical, veterinary and agricultural scientists, microbiologists, ecologists, mathematical modellers and epidemiologists, are needed to conduct collaborative and complementary studies that will unravel the dynamics of evolution and transmission of AMR. Methodologically, this includes culture-based, as well as genomic and metagenomic approaches, both *in vitro* and in *vivo* whilst using representative experimental models and study designs. Advanced methods for big data analyses may facilitate interpretation and risk assessment. Such studies should provide a better understanding of evolutionary and adaptive dynamics as well as risks and risk factors, in turn guiding interventions that could be of social, behavioural, biological, and/or technical nature. To identify and evaluate such interventions, the disciplinary width will need to be even broader, encompassing e.g., engineering, social science, humanities, economics, behavioural and political science. Such competence is also needed to identify and understand ultimate drivers (such as infrastructure, individual actions, laws and political decisions) that indirectly affect evolution and transmission of resistance. The work must be conducted in relevant settings and should always consider the broader One Health context when relevant, as well as the very different conditions encountered in different parts of the world, including high- and low-income countries. These are not only related to different levels of the burden of infections, hygiene, infrastructure and resources, but differences in e.g., behavioural and social factors which may also lead to different challenges and solutions.

Research and innovation objectives

1. Identify the main environments, mechanisms and drivers involved in the emergence of successful antimicrobial-resistant genotypes of different disease-causing microorganisms

While challenging to predict, the payoff from limiting or delaying the emergence of new successful resistance genotypes in the clinic can be substantial, thereby warranting dedicated research. Drivers (such as selection pressures) of evolution versus transmission of resistant microorganisms (see next section) often overlap, but the relative importance of e.g., different environments and pathways may differ profoundly. To direct interventions, research is needed on the fundamental evolutionary processes and the detailed mechanisms, mobilising elements, steps and bottlenecks involved. This also includes characterising the diverse, unknown resistome in a range of environments

(associated with humans, animals and external environments), and characterising genes with regards to e.g., diversity, microbial hosts, functions and mobility potential. Whole-genome sequencing of many more bacterial isolates of different species, including those today considered “uncultivable” will likely provide a frame for understanding the origin of many more resistance genes that are already prevailing in the clinics, possibly allowing generalisations of their evolutionary histories. There is a need to identify which environment types (i.e., hosts, external environments), drivers (including drug concentrations, fitness effects and mutation and transfer rates) and other biotic and abiotic conditions that favour mobilisation and transfer of resistance genes to pathogens/opportunistic pathogens. The competitive and cooperative interactions within the local microbiome (e.g., commensals, biofilms, rhizosphere) including bystander selection are likely to be critical. To understand the evolution and spread of successful clones, we also need to know more about the processes of adaptation involved in the spread and further (compensatory) evolution of novel resistant genotypes, and to assess how relative fitness of different genotypes varies between environments and conditions.

For fungal pathogens, which have considerably larger genomes than bacteria, there is much less genomic data available than for bacteria. This limits both our understanding of fungal resistance mechanisms, where and how resistance develops, and its transmission pathways. Broad, systematic sequencing efforts and adapted analyses pipelines would therefore be valuable as a basis for further research that in turn may guide mitigations.

With regards to selection, which may promote both emergence and further transmission of resistant microorganisms (see next objective), we need better methods to determine concentrations of antimicrobials (alone or in combination) that select for AMR in different environments. Such methods should also reflect the complexity of the matrix and of the microbiomes involved. Potential selectors to study are not only antibiotics or antifungals, but also metals and biocides and possibly other compounds. Bioavailability of antimicrobials in different media (e.g., water, soil, food, faeces) is also understudied, as are interaction effects. Effects of chemical agents and other factors that can accelerate horizontal gene transfer is also important to study.

A resistance factor only becomes a health problem when it is present in a disease-causing microorganism that infects humans, domestic animals or crops. The ecological connectivity between different external environments (including wildlife), domestic animals and the human microbiota therefore needs further study, not the least when it comes to directionality of transfer. This may, for example, involve molecular source tracking methods. The transfer of bacteria between humans, animals and the environment is of course not only relevant for the emergence of new forms of resistance, but also for the further spread of already well-known and problematic strains (see next objective). Experimental studies as well as modelling may be valuable in this context.

Social factors ultimately influence many of the direct drivers of the evolution and transmission of resistance (next section), including selection by antimicrobials.

Understanding the role of behavioural and social structures in these processes is also the basis for effective interventions (see last section). It is therefore critical to investigate how social factors, all the way from broad systemic issues (sociology, economics, politics) to individual behaviour, are linked to different proximate drivers.

2. Understand the directionality and scale of transmission of resistant microorganisms in and between humans, animals, and the environment, and identify critical routes and underlying drivers of transmission

Transmission within and between One Health reservoirs is still poorly understood, with key knowledge gaps specifically related to the directionality and quantity of transmission. Novel methods, also including model systems, are likely needed to efficiently assess both of these aspects. It is of particular interest to 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. It should be acknowledged that there may be routes whose contribution are currently underestimated. Efforts should include quantifying food, wastewater and waste materials as vehicles for resistance genes and resistant bacteria and fungi. Similarly, understanding the scale of transmission (local, national, regional, global) needs more attention. Methods that can better utilise Big Data, including artificial intelligence, may become useful to create models that take into account the many factors that can influence transmission. Still, we should always recognise the value of well-controlled, simple experiments, as well as the need to validate models empirically.

We need to better understand the strongly variable abiotic and biotic selection pressures that microorganisms face when moving across different milieus, transmission routes that sometimes can be quite complex, with bottlenecks that are still unknown. The relative contribution of different antimicrobials in maintaining or transmitting different resistant microorganisms in and between humans, animals and the environment needs to be better characterised. This also includes the use of different formulations, routes of administration and treatment regimens (see also the section on therapeutics). Bioavailability, competition with other microorganisms, and variable abiotic factors and selection pressures may also strongly influence their effect. Antimicrobials of special importance in human medicine may need particular attention to minimize the risk of AMR transmission from animals to humans. 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 within and between different reservoirs (including patients, healthy populations, livestock, crops, and the broader environment).

While relatively much data has been collected in recent years on the release of resistant microorganisms into different external environments, considerably less is known with regard to the reciprocal transfer to humans. Studies that characterise exposure levels in e.g., food and water are warranted, but even more needed are studies that can link different environmental exposure levels to colonization, and in the end also to disease outcomes. This research is critical to investigate to what extent there is a feedback loop

to humans (and/or domestic animals) or if environmental pollution with resistant microorganisms often is a “dead end”. Here, studies need to be conducted both in conditions representing high-, middle-and low-income countries, as variable level of sanitation and hygiene measures is likely to greatly influence risks. Social factors, including behaviour, underlying the (sub-optimal) transmission control are equally important to investigate. Exposures may also be influenced by changes in climate, e.g., by increased heavy rain events leading to sewer overflows, or flooding, and/or favoured by higher temperatures (e.g., *Vibrio*). The role of wildlife (including non-vertebrates) in the life cycles and transmission of various pathogens need better investigation. This also includes long-range transport with e.g., migrating birds, and classical zoonotic diseases (e.g., *Salmonella*).

Environmental surveillance with the objective of assessing transmission risks should be developed and intensified (environmental surveillance with the objective to assess the regional resistance situation in human and animal populations is covered under the surveillance theme). Urban (waste) water systems, aquaculture and manure-soil interactions represent some of the pollution-routes that are highly relevant to investigate, but surveillance on the exposure side (crops, food, water) is also warranted. It should be possible to build on the infrastructure to monitor Sars-CoV-2 in wastewater that has been developed in many countries during the pandemic. Both metagenomic and culture-based surveillance may prove useful.

The role of hospital, primary care, versus community and environmental transmission of various disease-causing microorganisms, and the value of increased hygiene needs more focus. For example, initiatives to control transmission of ESBL 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. Overall, the role of asymptomatic carriage in society needs further attention.

3. Identify, design and evaluate technical and social interventions to control the emergence and transmission of resistance based on an understanding of the relative importance of different sources and drivers

Evolution and transmission of AMR could be prevented, reduced or delayed through both technical and social interventions (see also the section on preventive & mitigating interventions). The basis for identifying suitable interventions should be empirical and modelling data on the quantitative, relative contribution from different pathways and drivers (as outlined under the previous two objectives). Such anchoring is critical, as (costly) interventions that focus on sites or drivers of limited relative importance will lead to waste of resources and lack of effect (cost-effectiveness is important). Interventions that are desirable may, however, not always be practically feasible. Hence, research on prioritising interventions need to weigh in technical, geographical, economic, social, political and ethical concerns, including value- and norm-conflicts. Research may also be needed to optimise or facilitate the implementation of identified interventions, i.e., improve technologies, reduce associated costs or increase incentives for important actors.

As selection pressure from antimicrobials is a recognised driver of AMR, research aimed at optimising the use of antimicrobials is key. Social sciences contribution is particularly relevant in identifying, and tailoring actions aimed at tackling these needs. This includes better use of diagnostics and new therapeutics and treatment strategies (covered in other chapters), but also extends to e.g., transmission control and other measures that reduces the overall need for antimicrobials in both animals and humans, including tools that stratify risks for patients and hence need for (prophylactic) antimicrobials. Exploring the links between antimicrobial exposure, dysbiosis-related negative health effects and resistance could also be valuable for optimising use. Research addressing the collective action problem associated with antimicrobial use in all sectors on different levels is needed. To create incentives for limiting antibiotic pollution, international standards for "safe" emissions from manufacturing (and other sources) are needed (see also the chapter on Therapeutics and Preventive & Mitigating Interventions). Such standards could be applied in both legally binding settings and in reward-based systems (e.g., procurement). The role of antibiotics in hospital wastewater and domestic sewage, and the potential need to mitigate associated risks e.g., through appropriate waste management strategies and source control also needs further attention.

Globally, AMR is more closely correlated to lack of sanitation than to reported use of antimicrobials. The multiple benefits of improved water, sanitation and hygiene (WASH) that also included expected reductions in AMR warrants more research on sustainable WASH solutions that can be applied in low- and middle-income countries (see also the chapter on Preventive & Mitigating Interventions). This includes both technical, economic, and political aspects, and the evaluation of best available technologies adapted to context.

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 taken to circular economy. An integration of biological, environmental, sociological, epidemiological and economic data could identify important drivers of emergence and transmission, in turn informing interventions. Inherent to this analysis is the mapping of the distribution of strains and plasmids of public health importance, which could generate contextual evidence for the association between healthcare networks, food production, trade, infrastructure and certain genomic lineages of important nosocomial pathogens.

Models of AMR dynamics in different food and plant production systems could help us understand the role of different husbandry production/farming systems, including the aspect of biosecurity. It should, for example, be investigated which sanitary measures are need for manure used for fertilisation and how biological and/or physico-chemical manure treatment (which is now mainly used for environmental reasons to remove ammonia which can pollute the environment or to produce biogas via fermentation) can be optimised to reduce the burden of antibiotic residues and of AMR determinants.

On the exposure side, we need more knowledge on interventions that prevent colonisation, domination of the microbiota, and ultimately infection of the host by

resistant organisms. This also involves research on food security, the effect of international travel/migration, and which types of contact that lead to transmission. The use of artificial intelligence and digitalised support could potentially assist transmission control on different levels and in different settings.

Finally, to further motivate actions on a political level, we need better and up-to-date estimates on the impact on AMR of different systems of healthcare, animal production, global trade and the society as a whole. Such estimates should compare the costs of action and non-action (taking into account external factors).

Interventions for prevention and mitigation

Develop and improve interventions and innovative approaches to prevent and control the spread of Antimicrobial Resistance

The goal of this priority area is to reduce the emergence and spread of AMR using One Health interventions. In this context, interventions refer to all strategies, tools, programmes and actions that prevent or reduce the incidence, prevalence and dissemination of AMR. This can be through measures including infection prevention and control, promotion of responsible antimicrobial use, strengthening of health systems, promotion of vaccine uptake, community engagement for rational antimicrobial use, sustainable agricultural practices, prevention of environmental contamination with antimicrobials from various sources and public health measures such as water, sanitation and hygiene.

As reinforced by the COVID-19 pandemic, AMR prevention and interventions can fail unless these are addressed on a global and systemic scale. Interventions should involve relevant stakeholders and should pay particular attention to challenges in different geographical and cultural contexts, resourcing and contextual feasibility, and cost-effectiveness.

Introduction

AMR is primarily driven by misuse and overuse of antimicrobials in multiple sectors including human health, animal health, aquaculture and horticulture. In many instances, the environment can act to transmit and amplify resistance, providing a medium to disseminate resistant microorganisms and create ideal conditions for transfer of genetic elements encoding for resistance. The likelihood of inappropriate use of antimicrobials is higher when the need for antimicrobials is increased in conditions mostly associated with higher disease burden and poor legislative oversight. Therefore, effective interventions should address at least one of the following three aspects: reducing the need for antimicrobials, improving the appropriateness of antimicrobial use and decreasing the transmission of resistance.

AMR is complicated by several systemic factors, including the quality of health systems, robustness of agricultural production practices, environmental protection systems and investments in regulatory oversight. Therefore, interventions can be AMR-specific or AMR-sensitive. AMR-specific interventions directly address the issue of AMR while AMR-sensitive ones aim to influence the drivers of AMR indirectly. An example of an AMR-sensitive intervention is to improving access to appropriate sanitation facilities in a low-resource setting.

Adoption of a One Health approach is essential to develop effective interventions that cover clinical and veterinary medicine, agriculture, aquaculture, food production as well as waste management systems from both manufacturing and use where AMR can both develop and spread. As the introduction and use of new interventions are impacted by

different economic, cultural, contextual, and behavioural determinants, the strategies to tackle these barriers need to be equally diverse and adaptable to use in all One Health settings. For example, efforts to improve appropriate use of antimicrobials in human healthcare, should ideally be complemented by regulations to restrict the use of antimicrobials important for human health in veterinary medicine or agriculture. In addition, a One Health approach is crucial when studying AMR in the food system. AMR as well as antimicrobial residues can be passed on through the food chain if adequate measures are not introduced. At the country level, the food safety standards are usually established and enforced by departments specialised in health and/or nutrition. These may in many instances operate in isolation to the veterinary and agricultural departments overseeing the animal production process as well as environmental agencies or ministries controlling the antimicrobial emissions from farms or agricultural processing facilities. Therefore, if there is no alignment between the different sectors, AMR as a food safety issue cannot be effectively dealt with. With this in mind, and as with many complex challenges, one targeted intervention to address AMR may have limited impact, and a more holistic approach that considers the relevance of other sectors and its possible collateral benefits/damages should be considered.

Interventions to reduce the need for antimicrobials are mostly directed at reducing the incidence of infectious conditions in humans and animals. When the supply-chain of antimicrobials are not compromised, a higher incidence in infections or a higher likelihood of infections results in an increased requirement of antimicrobials, which can lead to higher selection pressure for resistance to emerge. Communicable disease control strategies, infection prevention and control (IPC) initiatives and biosecurity interventions to prevent outbreaks of infections in farms are more conventionally implemented interventions. Other emerging domains include the use of vaccines in reducing the incidence of infections. There is evidence that use of pneumococcal vaccines can reduce the need for repeated antibiotic therapy in patients suffering from chronic obstructive pulmonary disease. Good quality evidence about lower incidence of infections and reduced requirement of antibiotics post-vaccination are also available from poultry and aquaculture sectors. Another example of a novel intervention to reduce use of antibiotics is the use of probiotics. There is a growing body of research globally to show that probiotics can improve the health and quality of microbiome; and indirectly reduce the likelihood of infections.

Improving the quality and appropriateness of antimicrobial use will also contribute directly to reduction in selection pressure for new resistance to emerge. Antimicrobial Stewardship in healthcare delivery and animal health are the most applied interventions to reduce the inappropriate use of antimicrobials. Development and use of guidelines, robust regulatory oversight on the use of antimicrobials and improved access to diagnostics are all examples of strategies to limit misuse and overuse of antimicrobials. Innovative educational campaigns and training programmes to promote prudent use of antimicrobials among various stakeholder groups have also been tried out over the years, though there are challenges associated with measuring impact. The use of point-of-care diagnostics or rapid methods which can reduce the turn-around-time for antibiotic sensitivity tests (AST) are emerging themes (see also the section on Diagnostics and Therapeutics). Compilation of the results of AST, through systematic

methods or surveillance systems, can also inform the use of antimicrobials in various sectors.

Efforts to decrease the transmission of resistant organisms, antimicrobial residues or resistance genes are necessary to reduce the overall load of AMR. Hotspots for antibiotic use and emission have been identified within healthcare facilities, farms, pharmaceutical plants as well as waste-water treatment plants which provide ideal conditions for emergence of resistance and their proliferation. Interventions to restrict the transmission through effective containment strategies as well as remove antimicrobial residues from hospital and pharmaceutical wastewater have received considerable attention in the last decade. Methodologies to improve the overall efficiency of wastewater treatment plants (WWTPs) in dealing with residues and ARG have also been piloted, with varying degrees of success. Isolation strategies in healthcare facilities have been used to limit the spread of resistant organisms. Innovative methods to improve access to Water, Sanitation & Hygiene (WASH) in the community have also received attention, especially in the background of Sustainable Development Goals and the more recent COVID-19 pandemic.

There is tremendous scope for improving the design of interventions targeting AMR based on existing evidence, as well as testing new approaches and improving the uptake and impact of existing ones. Studies that research the feasibility, effectiveness and cost-value benefit are possible avenues for strengthening the pipeline for interventions directed at preventing or mitigating the AMR challenge. The impact of any intervention will depend on several factors beyond its efficacy in controlled conditions. For example, introducing a new vaccination strategy for aquaculture farmers will require several considerations such as the data on uptake and affordability among farmers, technical and administrative feasibility, opportunity costs for the intervention and effectiveness in reducing antimicrobial use and AMR. The intervention design should also be cognisant of the target stakeholder groups and align well with the priorities of communities and countries. The different stakeholders should be involved in the planning and design of the interventions through appropriate use of qualitative research methods.

Intervention research is closely linked to the principles of implementation science since the latter is all about translating evidence into policy and practice. Intervention and implementation research forms part of a continuum, which looks to improve the uptake of research in various forms. While interventions are mostly developed based on evidence generated in controlled environments or in the laboratory, implementation research tries to apply this in real-world settings. Once there is high quality evidence on the effectiveness, cost effectiveness and feasibility, scale-up and policy formulation becomes much easier.

However, when designing interventions to prevent and mitigate AMR, several equity issues should be considered such as the lack of access to antimicrobials in some parts of the world which still contribute to death due to lack of access rather than AMR. In addition, when antimicrobial stewardship interventions are designed in such contexts, strategies to ensure access to essential antibiotics must be built into the intervention. Similarly, and in some low-resource settings, small and medium scale farmers are unable

to invest in improving infrastructural biosecurity and waste management measures and thus resort to antimicrobial use as an infection preventative measure. Therefore, when standards, guidelines or certification systems are designed, it should consider the concerns of these small and medium enterprises.

Not all antimicrobial use is evident and fully understood. For example, antimicrobials (especially anti-fungals) are used extensively in horticulture for preventing disease in plants, but this is largely ignored while designing interventions. This is also true for antimicrobial emissions and several sources of AMR pollution are not fully identified or understood. The situation is complicated by the fact that disinfectants, biocides and even heavy metals can mediate the emergence of resistance. However, many interventions have so far not moved beyond the conventional considerations around healthcare facilities or pharmaceutical manufacturing plants. There are also several ecological niches which facilitate the evolution and transmission of AMR but are poorly mapped and thus overlooked when interventions are planned and tested.

Quantifying the impact of interventions to tackle AMR is also a challenge in many instances when implementation research principles are used in real-world settings. For example, in an intervention designed to improve the quality of diagnosis in blood-stream infections, it may be feasible to demonstrate a reduction in overall use of broad-spectrum antibiotics. But showing a sustainable reduction in AMR will be challenging in most scenarios. Similarly, a novel communication campaign to increase awareness about AMR may take a long time to show any improvement in the actual AMR situation. This affects our ability to prioritise interventions and direct resources. The scientific community is forced to depend on qualitative or non-objective criteria for deciding on the value-for-money interventions.

Research and innovation objectives

1. Evaluate opportunities, acceptability and feasibility of interventions in different countries/local contexts

Since the drivers and impact of AMR are unequal and different across sectors and populations, different populations and target stakeholders will have different needs for interventions, based on socio-economic backgrounds, existing regulatory structures, cultural factors and systemic organisation. Therefore, mapping the needs of stakeholders and populations, evaluating technological gaps, assessing systemic capacity for uptake of interventions and exploring the regulatory landscape in a specific setting become an important research objective. The design of interventions, including the design of novel regulations and legislations, is closely linked to the priorities of the stakeholders and populations and feasibility in the local context. Research should contribute to identifying potential strategies (including advocacy efforts or communications) that could ensure the acceptability of the interventions among the relevant stakeholders.

Acceptability and feasibility are important aspects which determine the success of an intervention in any context. For example, antimicrobial stewardship efforts led by non-

prescribers may not work well in many cultures that are traditionally hierarchical. Acceptability of interventions is also related to risk perception. Asking a poultry farmer to invest on improving the infrastructural and operational biosecurity measures may not be successful if the farmer is unable to understand the real risks associated with use of antimicrobials. Feasibility of interventions to prevent or contain AMR is dependent on administrative, financial and technical considerations. For example, film-array based diagnostics may be valuable for faster diagnosis of resistance and guiding selection of appropriate antimicrobials; but if the cost of the diagnostic platform is unaffordable to the healthcare system of the country or there are supply-chain constraints, it may affect feasibility significantly. Social sciences' contribution is particularly relevant in the evaluation of acceptability and feasibility of interventions.

2. Design and test interventions based on new and existing evidence and new technologies to prevent and mitigate AMR

While studies evaluating the uptake and compliance of existing interventions are important, the development of novel and innovative interventions are needed to better prevent and control the spread of AMR. Designing of interventions which build on new technologies provide an opportunity to foster and improve the tools available for global action on AMR. For example, Healthcare Associated Infections (HAIs) are a priority for designing new interventions since these infections can drive the use of the reserve category of antimicrobials. It has been shown that biofilms and colonisation in the hospital environment drive many HAIs. There is an urgent need to find effective and affordable solutions to reduce the risk of biofilm formations and colonisation, including provision of clean water in healthcare delivery settings. Re-engineering hospital surfaces and medical instruments are examples of possible interventions.

Reducing the load of infections and thereby the requirement of antibiotics is another priority for designing interventions. During the COVID-19 pandemic and several dengue outbreaks worldwide, the misuse of antibiotics associated with treatment has been largely reported. Therefore, every encounter with the healthcare system increases the probability of antibiotics being used or misused, even though the aetiology of the infection may be viral. Vaccines, against viral or bacterial infections, can reduce the incidence of infections and use of antimicrobials. There are multiple vaccines targeting AMR pathogens (e.g., *S. aureus, P. aeruginosa* and *A. baumannii*) currently in the development stage. Learnings from vaccine technologies and platforms developed during COVID-19 will likely lead to increased production of bacterial vaccines. The impact of those vaccines on the use of antibiotics needs to be studied. The effectiveness of novel vaccines in animal health for reducing the use of antimicrobials can also be evaluated.

Interventions and prevention strategies should be co-designed with the end-users and relevant stakeholder groups. Methodological robustness is a priority during the testing phase, to ensure validity of the results. The methodology for testing should consider selection of appropriate population and adherence to all statistical and epidemiological principles, to ensure good uptake by all the stakeholders and users.

3. Estimate the impact and cost-effectiveness of new interventions and prevention strategies

Quantifying the impact of interventions on the AMR situation is quite challenging, primarily because of the long time it takes to significantly reduce levels of AMR. Antimicrobial use or disease incidence are usually taken as surrogate markers for indirectly measuring the AMR burden, in the absence of appropriate metrics to document changes in AMR. Even more difficult is to measure the benefits associated with AMR-sensitive interventions. For example, the collateral benefits (in terms of improvement in AMR situation) associated with efforts to increase access to WASH in community settings are difficult to quantify. Though AMR is considered a systemic issue, investment in strengthening systems may take a long time to yield sustainable results in terms of reduction in levels of AMR. Lack of understanding regarding impact can possibly result in the policy makers not prioritising AMR interventions. Therefore, developing valid metrics and measurement strategies for the success of AMR interventions is an issue which should be addressed at the earliest.

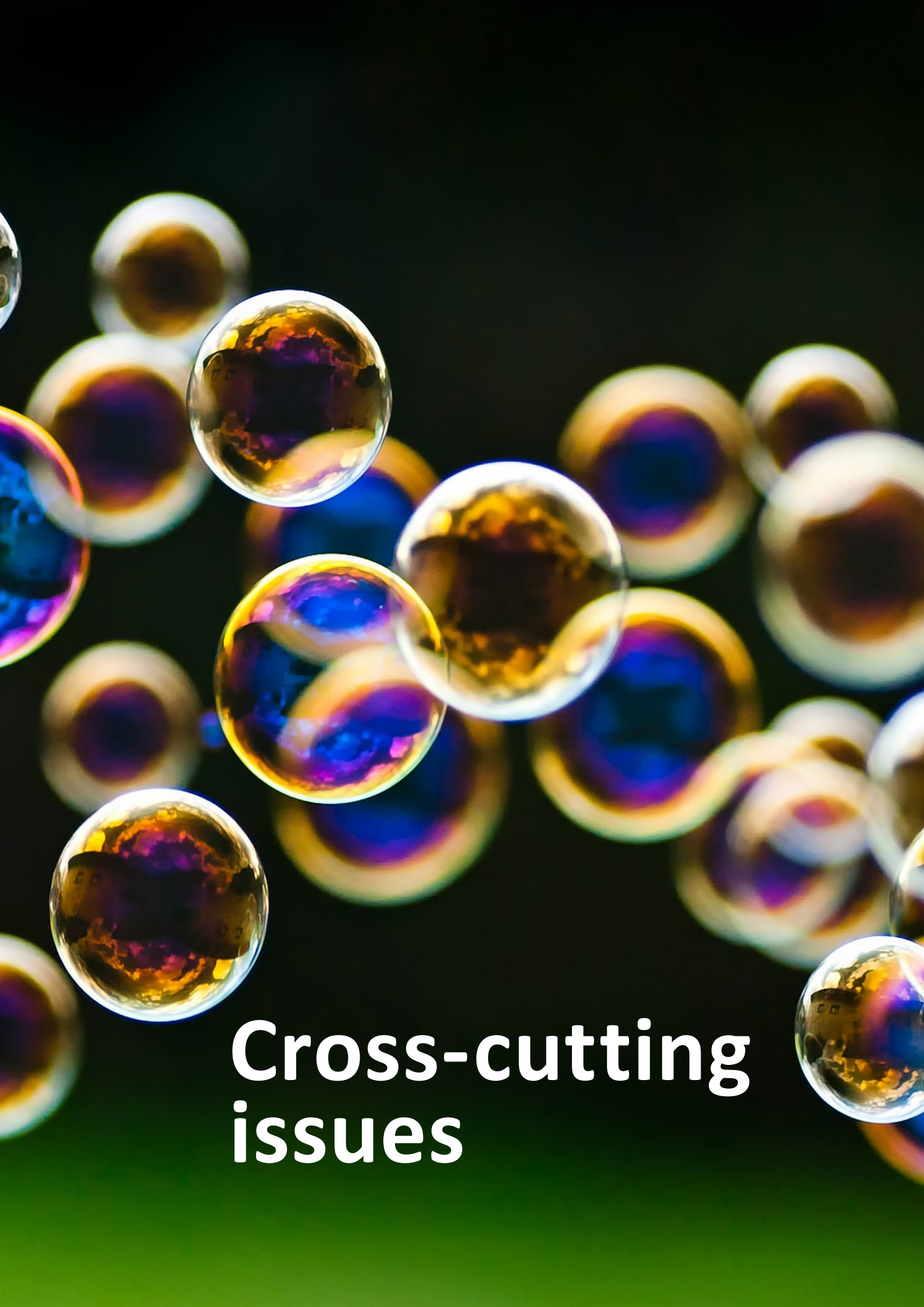
Evaluating cost-effectiveness of AMR interventions is another challenge that needs to be addressed. To be sustainable and scalable, the benefits of the intervention (decrease in Human or Animal morbidity and mortality, cost-savings to the patient, healthcare facility and to the healthcare system) should be higher compared to costs of implementation. Research should develop new methodologies to assess the cost effectiveness of interventions, and standardised methodologies like Cost per Disability-Adjusted-Life-Year (DALY) averted or Incremental Cost-Effectiveness Ratio (ICER) should be explored for evaluation of cost effectiveness of novel interventions. There is a wide perception that AMR interventions are not cost-effective, as most of the interventions involve investments to improve the strength of systems. For example, Antimicrobial Stewardship in healthcare delivery settings may require human resources for training, auditing and feedback. Similarly, introducing an operational biosecurity program or a vaccination program in a large farm, to reduce the need for antimicrobials, may also require significant investments. There is also a perception that there can be a loss of productivity associated with reduction in use of antibiotics in the agricultural sector. Therefore, research should develop robust methodologies that could discriminate between perception and facts, and convince local authorities, and stakeholders of the benefits associated with the interventions. Studies evaluating cost-effectiveness are required to advance quality improvement in healthcare delivery and agriculture, using an AMR lens.

4. Identify the parameters that should be considered to adapt a successful intervention to different settings, or to scale up interventions

AMR interventions are generally context-specific, and their success is determined by factors such as the demographic profile, systemic strengths and even socio-cultural norms. For example, adherence to guidelines and standard operating procedures is lower in some socio-cultural contexts. Potential for scale up might also be limited in countries where the health system is not centralised. Therefore, interventions that have been successful in one context or population, may not be successful in another. Implementation research will be needed to investigate how the interventions could be

adapted to other local conditions, resource availability and systemic capacity. As with the design of an intervention, the adaption process should also be based on feedback from the target stakeholders. Several revisions may be required on the basis of rapid testing on a small scale, to ensure a high level of acceptability and validity.

Adaptation is usually a multi-stage process guided by a panel of experts. Even though some of the interventions may look feasible and scientifically valid, the importance of testing the intervention in context should not be lost on those who are responsible for developing these interventions. For example, certification programs for farms or animal products cannot be the same across different countries. Though some certification systems for AMR have been successful in specific countries, an iteration and repeated piloting may be required to ensure success in regions with poorer lab capacity or lack of investment in improving agricultural practices. A similar format of adaptation is required for interventions on antimicrobial stewardship or use of guidelines in treating infections in animals. The intervention should be based on local conditions and requirements, though informed by data on the intervention working in other contexts.



Cross-cutting issues

Focus on four cross-cutting issues

Considering the complexity of AMR, some specific issues will be applicable to all the thematic areas. Those cross-cutting issues are expected to be taken into account in the design, development and implementation of the research for each of the areas. Cross-cutting issues are developed below.

Antimicrobial resistance: a phenomenon driven by social factors[32]

Human activities - lifestyles, farming methods, eating habits, mobility, acquisition of new techniques - have direct repercussions on the environment and consequently on the microbial environment and on the health status of the populations concerned. It is therefore crucial to involve the social sciences at all stages of the AMR research process, alongside the life sciences. In a similar manner to life sciences, social sciences encompass a range of disciplines with different scales and scope, each of which can make distinct contributions to the research and innovation priorities to decrease the burden of AMR. In the framework of the One Health AMR Partnership, social sciences will include sociology, psychology, anthropology, politics, arts and humanities, economics, ethics, law and implementation/management science (see below). This plurality of social science disciplines can produce evidence on how best to monitor, manage and mitigate AMR. The disciplines can offer an understanding of the phenomenon of antimicrobial resistance not only as a biological issue but also as a social issue that is affected, for example, by behaviour, law, culture, ethics, and management science. The plurality of approaches within the social sciences places them front and centre of any meaningful plan to address AMR and they are positioned to respond to AMR as a problem that manifests in different ways in different places and over time, rather than as a uniform phenomenon. Although AMR is recognised as a global phenomenon, it affects countries to different degrees, reflecting their respective economic, social and environmental contexts and challenges. This perspective can not only shed light on parameters that are predominantly socio-economic but also can contribute to the understanding of the biosocial dynamics of AMR from a One Health perspective. Social sciences will allow, for example, to better understand the individual (age, gender, genetic, medical background) and societal drivers of AMR transmission, to identify the social barriers preventing the uptake of preventative or mitigating interventions, and to propose solutions to overcome those barriers.

The need for interdisciplinary research where life sciences and social sciences are combined to find innovative solutions is well recognised. However, to date, both life scientists and social scientists have worked on multiple aspects of AMR, but often in isolation. JPIAMR and, the candidate One Health AMR partnership, intend to encourage multi- and inter-disciplinary research across the social and life sciences. In line with this idea, social science priorities have been included in the research and innovation objectives (Table 3 and 4). In addition, a group of experts has been convened to propose solutions to encourage the active collaboration of social scientists with life scientists and overcome the current difficulties faced by social scientists when trying to participate in calls for projects.

[32] Adapted from a draft working paper by the OH AMR Social Sciences working group, describing the potential contribution of Social Sciences to curb AMR.

Table 3. Examples of the research and innovation priorities in social sciences addressed in the different thematic areas. (Priorities associated with Implementation Science are listed in Table 4)

Thematic Area	Social Science Relevant Contributions
Therapeutics	➢ Maximise the probability of a new drug ultimately succeeding in the clinic and shorten the time for this to occur within an acceptable ethical framework. ➢ Define a proper ethical balance between the environmental cost associated with the use of some antimicrobials (and a potential indirect human cost in the future years), and the more immediate human cost associated with the potential morbidity and mortality in patients in absence of efficient treatments. ➢ Develop new economic models to encourage private sector investment in drug discovery/development and address regulatory hurdles (this objective will be conducted in synergy with the Joint Action 2 on AMR and HERA). ➢ Identify the local needs of the end-users (storage conditions, knowhow, infrastructure, availability of diagnostics) during drug formulation and production to preserve their efficacy for patients in all contexts. ➢ Estimate the effectiveness of novel therapeutic solutions for populations with different backgrounds (age, genetic, ethnic, economic and medical background).
Diagnostics	➢ Facilitate and estimate the uptake and effectiveness of diagnostics for populations with different backgrounds (age, genetic, ethnic, economic and medical background). ➢ Adapt existing diagnostic tools to different One Health settings, to different cultural characteristics, and to the specificities of different territories. ➢ Identify the local needs of the end-users (storage conditions, rapidity, and accessibility to knowhow, infrastructure and internet) during the design of diagnostic tools to preserve their access for patients in all contexts.
Surveillance	➢ Investigate the inequities in AMR burden in different geographical and socio-economic settings. ➢ Correlate the surveillance data with social profiles and behaviours. ➢ Identify the local needs of the end-users (knowhow, infrastructure and internet access) during the design of surveillance tools to warranty their use in all contexts. ➢ Adapt existing surveillance systems to different One Health settings, to different cultural characteristics, and to the specificities of different territories. ➢ Develop communication strategies and methods to promote the use and analysis of surveillance data
Transmission & Evolution	➢ Investigate how social factors, all the way from broad systemic issues (sociology, economics, politics) to individual behaviours constitute drivers of AMR evolution and transmission. ➢ Use transmission to estimate the effectiveness of interventions.

Interventions for prevention and mitigation	➢ Evaluate the different requirements for interventions, based on socio-economic backgrounds, existing regulatory structures, cultural factors, behaviours and systemic organisation. ➢ Investigate how the local conditions (administrative, financial and technical considerations) could modify the feasibility and sustainability of proposed interventions. ➢ Develop methods and approaches to ensure intersectoral and interdisciplinary management of AMR burdens and design interventions that could break the silos between the different One Health settings. ➢ Propose economic and contextually appropriate AMR-specific policy interventions. ➢ Understand the drivers to mobilise actions on AMR in formal structures (government, legislation), as well as informal structures (social networks, media, social media, professional networks), and use this information to develop and evaluate strategies to promote such actions.

From research to uptake: the role of implementation/management science

Implementation/management science is a social science discipline. While interventions (including Therapeutics and Diagnostics) are mostly developed and evaluated in controlled environments or in laboratories, implementation science aims to identify methods to apply this in real-world settings. Implementation science is the study of methods to promote the adoption and integration of evidence-based practices and interventions, into routine health care and public health settings to improve population health impacts[33]. The main readouts should be acceptability, adoption, cost, coverage, and sustainability. Intervention research and implementation science form part of a continuum, which seeks to improve the uptake of research in various forms. The candidate One Health AMR partnership will encourage the involvement of key stakeholders even at early research stages and the inclusion of implementation science to facilitate the uptake of research results and guide policy[34]. In line with the idea, implementation science priorities have been included in the research and innovation objectives (Table 4).

[33] Definition adapted from NIH: https://cancercontrol.cancer.gov/is/about
[34] This objective will be conducted in synergy with the Joint Action 2 on AMR.

Table 4. Examples of the research and innovation priorities in implementation sciences addressed in the different thematic areas.

Thematic Area	Implementation Science Relevant Contributions
Therapeutics 	➢ Identify barriers and identify and evaluate strategies to improve the acceptance of alternative therapeutic strategies by patients as well as by clinicians, and by other health care professionals. In particular, identify how local practices in medicine could affect the acceptance of new treatments and new treatment protocols. ➢ Identify barriers and identify and evaluate strategies to improve the acceptance of novel therapeutic strategies by regulatory authorities and by public and private medical insurance systems. ➢ Identify barriers and identify and evaluate strategies to improve the uptake of new therapeutic strategies such as cost-effectiveness calculations and price acceptability, better control of drug quality and marketing/sales, as well as improved accessibility in local markets. ➢ Understand how current national regulations and enforcement (or absence of regulations/ enforcement) and national and regional organisations (for example the economic weight of some local pharmaceutical producers, and the access to a structured health care system) influence the uptake of new therapeutic solutions. ➢ Understand and address the socio-economic challenges associated with the production, distribution and access of novel antimicrobials by studying the structural role played by key stakeholders (e.g., institutional, commercial, legal, ethical, end-users) across the value chain
Diagnostics 	➢ Identify barriers and identify and evaluate strategies to improve the uptake of the diagnostic tools such as cost-effectiveness, price acceptability, reimbursement mechanisms and non-financial incentives. ➢ Design and evaluate strategies to promote awareness of patients and stakeholders (including drug prescribers) on the value of diagnostics in AMR prevalence and antimicrobial usage. ➢ Investigate which behavioural, cultural, infrastructural and economic factors need to be changed to improve implementation and acceptance of new diagnostics by the relevant end users.
Surveillance 	➢ Use robust surveillance data to design cost effective models based on evidence. ➢ Identify difficulties for implementation of open access tools for data sharing due to infrastructure capacity limitations and/or laws/regulations and intellectual property constraints. ➢ Define a minimum, cost-effective sampling framework.
Transmission & Evolution 	➢ Investigate incentives and counter-incentives for different actors that have the ability to contribute to the reduction of risks for resistance evolution and transmission with regard to actions that could reduce AMR and, identify and compare different types of cost for activity and non-activity.
Interventions for prevention and mitigation 	➢ Develop methods to enhance the acceptability of the interventions among the relevant stakeholders. ➢ Investigate which behavioural, cultural, infrastructural and economic factors need to be changed to improve implementation and acceptance by the relevant end users. ➢ Identify the parameters that should be taken into account while planning to adapt a successful intervention to different settings, socio-economic contexts and other contexts or populations, or while planning to scale up interventions

From research to innovation

While research is urgently needed to provide new solutions to curb AMR, the transfer from research to innovation remains particularly challenging. In addition to the classical barriers to innovation (networking, Intellectual property issues, funding valley, lack of understanding of the market and route to translation from academic researchers…), the transfer to innovation faces additional challenges in AMR research, such as the low return in investment in developing of antimicrobials, which is a barrier to industry investment. In order to avoid the rapid development of resistance against new treatments, new therapeutic solutions are often safeguarded and restricted to clinical cases which do not respond to classical treatments. For these reasons, the development of antimicrobials may not appear attractive to pharmaceutical companies, and a real economic risk exists for the SMEs who are still the biggest contributors to innovation in the development of pre-clinical antimicrobial agents[35]. In addition to drug development, innovation is critical in the field of diagnostics and surveillance as well as for the prevention of AMR, where, for example, the creation of new techniques could be developed to combat drug resistance in drug hotspots such as wastewater treatment plans. The progress of artificial intelligence (AI), big data mining and cloud computing may also facilitate the analysis of surveillance data in real-time and promote the exchange of information to facilitate timely clinical decision making in human and veterinary medicine. The candidate partnership One Health AMR aims to address the innovation priorities in each of the thematic areas (table 5). In addition, specific actions, will be undertaken during the life of the partnership to encourage and facilitate the uptake of research results by innovators (measures encouraging the participation of private companies in funded projects, activities favouring the exchange of results and the uptake of research results among others).

[35] World Health Organization (2021), *Antibacterial agents in clinical and preclinical development: an overview and analysis*, ISBN 978-92-4-004765-5

Table 5. Examples of innovation priorities addressed in the thematic areas.

Thematic Area	Innovation priorities
Therapeutics	➢ Development of innovative therapeutic solutions up to preclinical development and early phase clinical trials. ➢ Development of new bioinformatic tools & software to enable modelling of key signalling pathways, and novel target discovery. ➢ Development of new approaches to streamline and de-risk both preclinical development and early phase clinical trials. ➢ Definition of new complementary endpoints to evaluate the efficacy of treatments (especially alternative treatments) ➢ Development of new economic models (objective to be explored in collaboration with the Joint Action 2 on antimicrobial resistance and HERA, the Health Emergency Preparedness and Response Authority).
Diagnostics	➢ Development of affordable, accessible and ideally rapid point-of-care or point-of-need diagnostics. ➢ Development of new bioinformatics and AI solutions to identify new diagnostic or prognostic markers. ➢ Demonstrate the value, utility and benefit of diagnostics.
Surveillance	➢ Development of novel and rapid technologies that allow accurate determination of abundance and diversity of drug-resistant microorganisms, antimicrobial resistance genes and their associated mobile genetic elements and their continuous evolution (i.e., temporal and condition-driven modifications) in both humans, animals, and in the environment. ➢ Development of online, real-time and automated analysis of the surveillance data. ➢ Development of standardised approaches to identify and measure the use of antimicrobials and control of AMR ➢ Development of AI methods for the collection, analysis and sharing of surveillance data. ➢ Improvement of environmental surveillance as a resource to assess the local and regional AMR burden.
Transmission & Evolution	➢ Development of AI methods for big data analyses and treatment selection solutions.
Interventions for prevention and mitigation	➢ Development of new tools to prevent and mitigate AMR (including but not restricted to development of probiotics, systems to prevent biofilms and bacterial and fungal colonisation, removal of AMR genes and bacteria from Wastewater treatment plans and other hotspots).

AMR, a global issue

Levels of AMR are particularly critical in Sub-Saharan Africa, and in South Asia[36]. As illustrated by the COVID-19 pandemic, pathogens circulate without recognising borders. Limiting the circulation of pathogens, microorganisms or their genes is elusive. For this reason, the fight against AMR should be coordinated worldwide. In this context, WHO developed in 2022 a global research agenda for antimicrobial resistance in the Human Health sector while WHO, FAO, WOAH, and UNEP joined their effort to develop a One Health Priority Research Agenda for Antimicrobial Resistance[37]. The identification of research and innovation objectives for the One Health AMR Partnership was done in alignment with these organisations in order to ensure synergy and complementarity. In this context, a specific attention has been paid to cover the priorities of both High-Income Countries (HIC) as well as Low- and Middle- Income Countries (LMICS). In addition, the research and innovation objectives also address how the local contexts (prevalence of resistance genes, different infrastructures, laws, culture, climate, cultural frameworks, therapeutic systems, access to care, and resources) should be considered while developing new interventions, new treatments or new diagnostics (table 6).

[36] Murray C.J.L et al. (2022). *Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis*; DOI: 10.1016/S0140-6736(21)02724-0
[37] Publication of both agendas is foreseen during the last trimester 2022/ beginning of 2023.

Table 6. How issues related with the international spread of AMR are tackled in the proposed Research and Innovation Objectives.

Thematic Area	International context
Therapeutics	➢ Development of new methods to promote the accessibility of the drugs in local markets. ➢ Understanding how the current national regulations and enforcement thereof (or absence of regulations/enforcement) and national and regional organisations (in particular the economical weight of some local pharmaceutical producers, and the access to a structured health care system) could influence their uptake. ➢ Development of new economic policies (such as economic incentives) that should also guarantee the availability of new and old drugs in low-resource areas. ➢ Development of solutions to better control drug quality, marketing/sales and use, in particular with reference to the production of generic drugs, unlicensed internet sales and the black market in antimicrobials that facilitate the use of poor-quality drugs (falsified, substandard, or degraded) in different national contexts. ➢ Development of new techniques for the disposal and recycling of unused antimicrobials in different local contexts should also be sought.
Diagnostics	➢ Understanding which diagnostic technologies and methods can be successfully implemented in resource-constrained-settings. ➢ Understanding of the differences that exist between the needs of HIC and LMICs and develop strategies to approach the use of diagnostics in different cultural and socio-economic settings.
Surveillance	➢ Development of surveillance systems in global and local settings. ➢ Development of One Health AMR and Antimicrobial use/Antimicrobial consumption surveillance applicable in the medium term and at a global scale, within available resources. ➢ Development of strategies to promote the alignment of and access to surveillance data and platforms between HICs and LMICs and between public and private sectors.
Transmission & Evolution	➢ Define the role of migration, tourism, infrastructures, climate and trade in the spread of AMR, taking the circular economy into consideration. ➢ Define the dynamics of AMR transmission at different scales (national, regional, global)
Interventions for prevention and mitigation	➢ Understanding of the needs for the interventions, based on socio-economic backgrounds, existing regulatory structures, cultural factors and systemic organisation. ➢ Design of context specific interventions based on the demographic profile, systemic strengths and socio-cultural norms. ➢ Identification of the parameters that should modified while adapting an intervention to other contexts or populations in function of the (local conditions, resource availability and systemic capacity

Annex I. Acronyms

AMR	Antimicrobial Resistance
AMU	Antimicrobial Use
AMC	Antimicrobial consumption
AST	Antibiotic Sensitivity Tests
CSA	Coordination and Support Action
CBP	Clinical Breakpoints
CPE	Carbapenemase-producing. Enterobacteriaceae
EARS-NET	European Antimicrobial Resistance Surveillance Network
EC	European Commission
ECOFF	Epidemiological cut-off values
EEA	European Economic Area
EJP One Health	One Health European Joint Programme
EMA	European Medicines Agency
ESBL	Extended Spectrum Beta-Lactamase
EUP AH&W	European Partnership on Animal Health and Welfare
DALY	Disability-Adjusted-Life-Year
FAO	Food and Agriculture Organisation of the United Nations
FDA	Food and Drug Administration
HAI	Healthcare Associated Infections
HERA	Health Emergency Preparedness and Response Authority
HIC	High Income Countries
ICER	Incremental Cost-Effectiveness Ratio

IPC	Infection Prevention and Control
JAMRAI	Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LMIC	Low- and Middle- Income Countries
MGE	Mobile Genetic Elements
MIC-PTA	Minimum Inhibitory Concentration–Probability of target attainment
MRSA	Methicillin-Resistant Staphylococcus aureus
OECD	Economic Cooperation and Development
PK/PD	Pharmacokinetic/Pharmacodynamics
SME	Small and Medium Enterprise
UN	United Nations
UNEP	UN Environment Programme
WASH	Water, Sanitation and Hygiene
WGS	Whole Genome Sequencing
WHO	World Health Organisation
WOAH/OEI	World Organisation for Animal Health
WWTP	Wastewater Treatment Plants

Annex II. Process to define the research and innovation objectives of the candidate One Health AMR Partnership

The candidate One Health (OH) AMR Partnership programme is expected to be launched in 2025. The Coordination and Support Action (CSA) DESIGN is in charge of the preparation of the candidate partnership, including the definition of the Research and Innovation Objectives. To do this, the mandate has been given to 5 working groups to better define the research and innovation objectives in each focal research area (Therapeutics, Diagnostics, Surveillance, Transmission & Evolution, and Interventions for prevention & mitigation).

Those five working groups are composed of JPIAMR SAB members, complemented by additional external experts when specific expertise was missing. Each working group was chaired by a JPIAMR SAB member, and coordinated by a representative of the CSA DESIGN. Monthly meetings with the chair and coordinator of the working groups enable an alignment between the different groups. Each working group was in charge of defining the challenges in the thematic area, and identifying specific research and innovation objectives that could be tackled in the future partnership.

To support the working groups in their tasks, a series of consultations have been launched during the first semester 2022, see below. Some consultations were relevant for a specific thematic group (such as the workshop on surveillance), while some of the consultations were crosscutting (such as the consultations on environment). The thematic group members were invited to play an active role during those consultations, and a report of the conducted activities summarised the main conclusions of the consultations.

Thanks to the feedback received, the working groups established this present document. To complete their work, and ensure openness and transparency the current version is now available for open consultation (launch of the consultation: 2 December 2022; Closure: 16 January 2023). The final document will be prepared based on the input received. The research and innovation objectives will first be adopted by the Joint Programming Initiative on AMR (JPIAMR) prior to the launch of the One Health AMR partnership. The document will be regularly updated during the lifetime of the partnership.

Consultations

Topic	Activities	Expected Timing	Targeted Audience	Expected Outputs
Initial General Consultation	Survey	15/03/22 to 19/04/22	Ministries, Stakeholders, Researchers, SME and Large enterprises	Feedback on the current JPIAMR SRIA as a point of reference
Second General Consultation	Survey	01/12/22 to 16/01/23	Ministries, Stakeholders, Researchers, SME and Large enterprises	Feedback on the first draft of the research and innovation objectives of the One Health AMR Partnership
Surveillance	Workshop	23/03/22 and 24/03/22	Ministries, Stakeholders, Researchers, SME and Large enterprises	Feedback on the surveillance thematic area
Intervention & Prevention	Round-Tables	13/06/22 and 14/06/22	Ministries, Stakeholders, Researchers, SME and Large enterprises	Feedback on the "Intervention and Prevention" Thematic Area
Antibacterial Resistance	Webinar	09/06/22	Early Career Scientists	New perspective on antibacterial resistance
Antifungal Resistance	Webinar	23/06/22	Ministries, Stakeholders, Researchers, SME and Large enterprises	Needs and Gaps on antifungal resistance
Antiparasitic resistance	Surveys Round-Tables	04/05/22 to 21/06/22 15/09/22	National Representatives/ research funders and Stakeholders Potential members of the OH-AMR Partnership	National willingness to include antiparasitic resistance in the scope of the One Health AMR partnership, mapping of the national funders able to fund research projects on antiparasitic resistance, mapping of the current national and international funding on antiparasitic resistance, identification of the research gaps and needs in antiparasitic resistance.
Antiviral resistance	Surveys Round-Tables	04/05/22 to 21/06/22 15/09/22	National Representative/ research funders and Stakeholders Potential members of the OH-AMR Partnership	National willingness to include antiviral resistance in the scope of the One Health AMR partnership, mapping of the national funders able to fund research projects on antiviral resistance, mapping of the current national and inter-national funding on antiviral resistance, identification of the research gaps and needs in antiviral resistance.

Vaccination	Webinar	17/06/22	Ministries, Stakeholders, Researchers, SME and Large enterprises	Role of the vaccination in antibacterial resistance prevention; Needs and Gaps regarding vaccination against bacterial diseases
Innovation in Therapeutics and Diagnostics	Round-Tables	21/06/22 and 22/06/22	Innovation funders, Ministries, Stakeholders, Researchers, SME and Large enterprises	Actions to be undertaken in the OH AMR Partnership to support innovation
Social Sciences	Working Group	During the whole consultation process	Researchers in social sciences	Understand and evaluate the contribution of the social aspects in the prevention and control of AMR
Environment	Round-Tables	22/09/22 to 27/09/22	Participants of the 6th scientific meeting on Environmental Dimension of Antibiotic Resistance (EDAR6)	Needs and Gaps related to environmental diffusion of AMR
Stakeholders	Meeting	June 2022 and December 2022	Stakeholder Network	Practitioners needs Feedback on draft of research objectives

Experts

The following experts have been involved in the five thematic groups (in alphabetical order):

- Ana Alastruey-Izquierdo, Instituto de Salud Carlos III, Spain
- Dan Andersson, University of Uppsala, Sweden
- Till Bachmann, University of Edinburgh, United Kingdom
- Rafael Cantón, University Hospital Ramón y Cajal and Complutense University, Spain
- Teresa Coque, Ramón y Cajal Institute for BioHealth Research (IRYCIS), Spain
- Tania Dottorini, University of Nottingham, United Kingdom
- Uga Dumpis, Pauls Stradiņš University Hospital, Latvia
- Sabiha Essack, University of KwaZulu Natal, South Africa
- Christian Giske, Karolinska Institute, Sweden
- Bruno Gonzalez Zorn, Complutense University, Spain
- Luca Guardabassi, University of Copenhagen, Denmark
- Claire Harpet, Lyon 3 University, France
- Tom Harrison, St George's University of London, United Kingdom
- Elena Ivanova Reipold, Foundation for Innovative New Diagnostics, Switzerland
- Geetanjali Kapoor, Center for Disease Dynamics, Economics & Policy, India
- Joakim Larsson, University of Gothenburg, Sweden
- Marc Lemonnier, Antabio, France
- Nilton Lincopan, Universidade de São Paulo, Brazil

- Jean-Yves Madec, ANSES, France
- Christian Menge, Friedrich Loeffler Institute, Germany
- Chantal Morel, University of Geneva, Switzerland
- Katherine Payne, University of Manchester, United Kingdom
- Luísa Vieira Peixe, University of Porto, Portugal
- Priscilla Rupali, Christian Medical College (CMC), Vellore, India
- Etienne Ruppé, University Hospital Bichat and University of Paris, France
- Jonathan Rushton, University of Liverpool, United Kingdom
- Constance Schultsz, University of Amsterdam, The Netherlands
- Kornelia Smalla, Julius Kühn Institute, Germany
- Jordi Vila, Hospital Clinic in Barcelona, University of Barcelona and Institute for Global Health, Spain