One Health AMR Partnership SRIA

DRAFT Research and Innovation Priorities

EDAR6 conference

Therapeutics

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

The focus of this priority topic is to improve current antimicrobial treatment by enhancing discovery and preclinical and early clinical development of novel antimicrobial treatment strategies and alternative therapeutics, 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 anti-infective compounds by proposing innovative regulatory procedures and by stimulating economic incentives while ensuring a high level of acceptability to patients, appropriate use and minimum impact on the environment. Preventive research (including preventive vaccination) will be the subject of the section on prevention and intervention.

Introduction

The fast spread of antimicrobial resistance requires the continuous development of new antimicrobial agents, and new antimicrobial strategies. The scientific challenge of developing new and innovative antimicrobial agents is a major factor contributing to the general decline in the production by pharmaceutical companies. The number of antibiotics and antifungals in the development pipeline has decreased to critical levels due to the difficulty to recuperate costs for drug discovery of antimicrobial agents. The availability and development of antimicrobial agents for use in the paediatric population and in Low- and Middle-Income Countries (LMIC) is even more limited, and appropriate studies need to be conducted to ensure availability of therapeutic treatments for this specific population and geographies. In the period 2019-2020, only 3 new antibiotics have been approved by either FDA or EMA. In 2021 up to August 2022, the situation is going even worst with no new antibiotics approved by neither FDA nor EMA. The WHO conducted a review of publicly available information[1] 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 and limited to new therapeutic entities (NTEs) 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[2]. A comparison between the report published in 2019 and the one of 2022 reveals that in three years, the number of antibiotics and/or combinations in phase 1-3 clinical trials decreased by 10%, underlying, if needed, the emergency of the situation. The challenge is even bigger for fungi, which are eukaryotes with a relatively high degree of phylogenetic similarity to humans and therefore offer relatively fewer differential targets that can be exploited for antifungal drug development.

Although it's important for academic laboratories to continue their research efforts to identify new therapeutics target, and new drug leads, more collaboration with pharmaceutical companies is needed to accelerate the transfer from the bench to the bedside of the patients[3]. Between 2008 and 2020,

[1] https://www.who.int/publications/i/item/9789240047655
[2] https://apps.who.int/iris/bitstream/handle/10665/330420/9789240000193-eng.pdf
[3] https://www.fda.gov/Drugs/InformationOnDrugs/

ENABLE, one of the project funded by the Innovative Medicines Initiative (IMI) has been fostering public-private partnerships (PPPs) to drive transformational advances in the way drug discovery and development of new antimicrobial agents are performed. However, in 2021, IMI has been replaced by the Innovative Health Initiative (IHI), which will develop a broader approach to healthcare, covering prevention, diagnosis, treatment, and disease management creating a risk that the funds for the discovery of new antimicrobials could be diluted in the future years. Other Funding initiatives, such as Novo-REPAIR[4], CARB-X[5], and GARDP[6] (two not-for-profit drug development organisations) also have a strong focus on the development of new antibacterial therapeutics but their funding support progressing drug candidates through to clinical development and do not include early discovery. For antifungals, the situation regarding the development of new agents is even worse, 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[7] 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 will be needed to maximise efficacy and protect against future resistance. A better control of the doses, and duration of treatment, and innovative combination of antimicrobials could prevent the appearance and transmission of antimicrobial resistance. 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 will not be released for use in veterinary medicine, agriculture or aquaculture. It is therefore essential that current treatment regimens in animal health and protocols for use in agricultural settings are improved, and that alternatives to antimicrobials that can be used to prevent and combat infections in both animals and agriculture are developed.

Challenges

A strong collaboration between different research disciplines is needed to offer innovative therapeutics solutions.

Research into antimicrobial therapeutics should include the development of alternative strategies such as non-traditional drugs that aim to kill or reduce the growth of bacteria and fungi (for example phages or endolysins), but also strategies that target virulence mechanisms, including the inhibition of adherence to host cells, blocking of toxins or the dispersal of biofilm structures, or strategies aiming to enhance the clearing capacity of the host, including therapeutic vaccination, immunomodulation and innovative delivery solutions. If COVID-19 demonstrated the benefit of developing alternatives strategies to fight against infectious diseases, the pandemic also revealed the need to improve education around and the acceptance of such strategies by patients as well as medical doctors, and other health care professionals. The development of alternative strategies should include social sciences research to understand the barriers to uptake and how these may be overcome. Work will also be needed to address the acceptance of novel strategies by regulatory authorities and by public and private medical insurance systems.

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

[5] *Combating Antibiotic Resistant Bacteria*

[6] Global Antibiotic Research and Development Partnership

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

Innovative strategies such as personalised medicine, system biology and computational sciences should be further explored. However, work is needed to fully realize the potential of these technologies for product development.

The search for new antimicrobials should stem from proven unmet medical need, rely on strong science and be transferable to drug developers to maximise the chances of reaching the patients. JPIAMR and the One Health AMR Partnership recognise the need to support collaboration between clinicians, academics and industry to facilitate cross-talk, exchange of views and to build capacity amongst the wide innovation ecosystem. Only then would it be possible to share knowledge, to transfer technologies and to grow the next generation of scientists.

The current portfolio of new antimicrobials is weak, as demonstrated by WHO. There are many reasons for this, including the difficulty of the science. But the market failure currently in place clearly plays a role in the limited investment from the private sector, which in turn limits capacity to translate fundamental discoveries in microbiology into antimicrobial drug discovery programmes. Health economic research could help develop models to address the financial issues while international coordination should be fostered to help streamlining regulatory processes.

Developing new antimicrobial agents or protocols should not be limited to chemical development and clinical trials, but should also consider the way the molecules or protocols will be accessible to the targeted population, including the underserved population such as the persons living in Low and Middle Income countries (LMICs). The accessibility of the drug in local markets, the price of the new drugs in comparison of former drugs, as well as the training of 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 antimicrobial development. In particular, the drug ability to be rapidly degraded while released in the environment could be a valuable addition to the development plan of new drugs. The environmental cost of the drug production should also been taken into account and reduced as much as possible.

Research and innovation objectives and activities

Identify new targets towards the discovery of novel antimicrobials

Discovery of novel antimicrobial agent classes, active against new targets and with acceptable pharmacokinetic and safety profiles, is complex. Research on early stages of antimicrobial discovery and development (i.e. prior to the clinical trial phase) are critical to deliver new and innovative antibiotics and antifungals based on traditional and novel technologies, including nanotechnologies. The application of “omics” technologies (e.g. genomics, metabolomics, proteomics, and transcriptomics) in combination with powerful bioinformatic tools would enable modelling of key signalling pathways in the host-pathogen interplay and could be useful to find new antimicrobial targets. Moreover, in order to identify new antimicrobial targets, research is needed to generate insights into the mechanisms of resistance, gene transfer, and adaptive microbial evolution (fitness and virulence), including the action and role of persistence, host–pathogen interactions and antimicrobial resistance reversal. Efflux pump systems should be considered in strategies for finding new targets, since they are involved in expelling drugs from bacterial and fungal cells. The search for inhibitors of the mechanisms of resistance, including inhibitors of efflux pumps, inhibitors of β-lactamases that cover critical gaps, (ie inhibition of metallo-β-lactamases) or inhibitors of aminoglycoside modifying enzymes, are all relevant approaches. The development of "hybrid" entities with different mechanisms of action (targeting different sites / metabolic routes) should also be considered.

Develop new chemical entities and scaffolds for novel agents and their delivery

Innovative synthetic biology or chemistry strategies to develop novel chemical scaffolds for antimicrobial agents active on validated targets but capable of overcoming resistance mechanisms are needed. For antibiotics this could include, for instance, identifying agents that inhibit peptidoglycan cross-linking and that are structurally unrelated to beta-lactams, which act on the same target but with different modes of action or new interaction sites, or the development of nanoparticles and nanostructures for targeted drug delivery. New methodologies that identify physicochemical properties of antimicrobial agents must be encouraged, as well as approaches affecting the ability of small molecules to enter Gram-negative bacteria. These novel approaches could complement the more traditional screening of chemical libraries (including library of natural compounds) and the structure guide design of new molecules. Novel chemical scaffolds require appropriate characterisation of physicochemical properties, but this is a time-consuming process. The rapid characterisation of new resistance mechanisms is also critical to this purpose. Other difficulties in finding compound candidates include solubility of compounds, stability, toxicity (including effect on the host microbiota), specificity, drug penetration to the site of infection, route of delivery and efficiency. Discovery of new antimicrobials could consider exploring "green chemistry" and biodegradable scaffolds, and enzybiotics, to minimise the environmental impact of antimicrobial production and use. The development of improved delivery methods such as inhaled antibiotics could improve the drug targeting and be easily accepted by the patients.

When developing new antibiotics and antifungals for veterinary medicine and agricultural sectors, capabilities of cross-resistance to antimicrobials for human medical use should be carefully evaluated. A guidance for such evaluation needs to be developed which include wildlife bacterial and fungal diseases and a comprehensive One Health approach.

Develop alternatives for antimicrobials

Alternatives to antimicrobials, which could be useful to complement the activity of antimicrobial agents, should be used to overcome and reduce resistance selection and adverse effects associated with antibiotic and antifungal use. Specific alternatives could address all parts of the infection life cycle, for example anti-virulence strategies, bacteriophages, endolysins and fungal viruses, enzyme blockers, nanomedical solutions, molecular scissors, antimicrobial peptides and peptidomimetics, anti-biofilm agents, prevention of sporulation (fungi) or host defence peptides. A further promising approach that could be potentiated is the modulation of the human microbiota, that has been explored to treat infections by *Clostridiodes difficile* but which could also have other preventive or therapeutic applications.

Studies aiming at understanding the barriers (including the social individual and societal acceptance of alternative strategies, and organisational constraints) to uptake those alternative strategies and how these may be overcome would be needed. Often the development of these alternative strategies is jeopardized by the lack of proper tools to measure their true potential and differentiation. Currently available guidelines rely on the gold standard Minimum Inhibitory Concentration (MIC) – Probability of target attainment (PTA) method to measure drug candidates' efficacy against fast-growing pathogens. Such dominance of the MIC-PTA method is a barrier to innovation since a significant part of products under development are not aimed to directly kill the bacteria or inhibit their growth and/or are not targeting fast-growing pathogens. Defining secondary/complementary endpoints to evaluate e.g., the efficacy against tolerant behaviours or time-to-cure could increase the differentiation margin. Studies aiming at defining new endpoints are needed, especially when a discrepancy is observed between the MIC-PTA data and the *in vivo* data. Finally, research is needed to understand the cost

effectiveness of alternative strategies to inform national policy guidelines and ensure a proper implementation of the new protocols.

Improve pharmacokinetics and pharmacodynamics of antimicrobials, including neglected antimicrobials

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

Facilitate the design and implementation of clinical trials

Developing a wide range of preclinical models, recapitulating specific or multiple disease pathophysiological states, for screening the effectiveness and toxicity of candidate drugs, the likelihood of resistance and predicting their success in clinics is still needed.

Clinical trials evaluating efficacy are difficult and expensive; they can be complicated by the absence of rapid diagnostic tests to facilitate patient recruitment, limited incidence of disease and by the need for combination therapy and prolonged patient follow-up. Antifungal clinical trials have the added difficulty in enrolling complex patients who have a multitude of clinical problems. New approaches to streamline and de-risk both preclinical development and early phase clinical studies could maximise the probability of a new drug ultimately succeeding in the clinic and shorten the time for this to occur.

Research should also support post-approval studies and contribute to build evidence for product use across relevant indications, for specific and underserved populations and for specific pathogens. This could also involve connecting networks across JPIAMR and One Health AMR Partnership Member States to drive the clinical and enabling science for international post-approval studies.

Use personalised medicine and artificial intelligence to improve therapies

Addressing research on personalised medicine and the careful targeting of antimicrobial agents could optimise their safety and cost effectiveness. Rapid diagnostics, including point of care diagnostics, are essential for optimal antimicrobial selection. Whole-genome sequencing technologies have improved the understanding of resistance and allowed an identification of resistance mechanisms in multiple organisms. Whilst recognising that presence of a resistance gene does not always equate with clinically relevant drug resistance, the introduction of resistance mutation databases would aid patient management, enabling personalised treatment. There is an urgent need for personalised management through drug resistance screening in certain patient groups. Implementation of personalised therapies

according to geographical and care appropriate settings, local epidemiology, age, gender, metabolism and clinical characteristics (including the simultaneous treatment against other pathologies) are needed. Furthermore, in order to enable such strategies, it is essential to address social and behavioural factors that contribute to personalised medicine.

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

Develop treatment protocols for new and existing antimicrobials to enable repurposing and combination therapies

The role of novel and innovative combinations of compounds (antimicrobial agents, and combination therapy using new/existing antimicrobials, and repurposed drugs) should be investigated in mitigating the development of antimicrobial resistance in fungal and bacterial pathogens, as well as in situations of co-infections. Research on combination treatments should address differences in pharmacology of the combined agents as well as potential adverse interactions, impact on microbiota, and cost effectiveness of the therapy. Persistence is a less studied area and the role of combination treatments to eradicate persistent organisms should be investigated in those infections that are clinically relevant and with a validated treatment outcome. Combination antimicrobial therapy to prevent the emergence of resistance (and enhance efficacy) is a proven strategy for an increasing number of bacterial and viral infections (for example, tuberculosis, HIV), 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 pharmaceutical industry and academia to the exploration and development of combination treatments of old and new antimicrobials - from early stage screening for development of combinations, including screening for new compounds in the context of partner compounds, through to pre-clinical investigation of combinations in careful PK/PD animal models, and clinical trials.

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

The decreased interest of pharmaceutical companies in the development of antimicrobials could potentially be overcome by implementing new policy measures including new economic incentives to fix the broken AMR market and unlock the innovation potential in antimicrobial R&D. The delinking of revenues from the volume of sales appears to be a promising approach to both guarantee a fair and predictable revenue for the drug developer while maintaining strict stewardship policy standards. Such incentive should only be made available to those medications that demonstrate clinical utility, whose boundaries must be precisely defined. Further economic research needs to help design the required international framework under which each country could provide its fair economic contribution to fix the problem. The development of new economic policies should also warranty the availability of new and old drugs in low-resource areas. Engagement with local LMIC stakeholders should be sought to optimize widespread access, distribution and implementation.

Establish new regulatory standards and assess how regulation modifies and influences production and use of antimicrobials

Research is needed to inform and drive national and international regulation. In particular, new data on antimicrobial degradation into the environment, and estimation of the risks of cross-resistance

between humans and animals should contribute to new regulatory standards for the development of new drugs. Techniques to estimate and reduce the environmental cost associated with the production for new antimicrobials should also be developed, and the implementation of those techniques should be encouraged by national regulation. In particular, research should contribute to the decrease in direct release of antimicrobial derivatives and resistant bacteria/fungi from pharmaceutical industry through the improvement of sewage and wastewater treatments from industries, and the development of novel bio-engineering methods to minimise the release and spread of AMR in the environment. New industrial methods to reduce and prevent additional contamination of the environment with resistant bacteria, fungi and antimicrobial residues could best be developed in partnership between academia and bio-sanitation engineering industries. In addition, techniques favouring the disposal and recycling of unused antimicrobials in different local contexts should also be sought. On the other side, it will also be important to understand how current national regulations (or absence of regulations) and national and regional organisation (in particular the economical weight of some local pharmaceutical producers, and the access to a structured health care system) could influence the uptake of new treatment protocols, new antimicrobial strategies, and the development of resistance against new antimicrobial agents. Research will be needed to propose solutions to better control drug quality, marketing/sales and use particularly considering generics production and unlicensed internet sales and black market of antimicrobials that facilitate the use of poor-quality drugs (falsified, substandard, or degraded) in different national contexts. The research policies should consider a One Health approach across agriculture/food production, environment, and healthcare.

Diagnostics

The goal of this priority topic is to stimulate the design, development, evaluation and implementation of diagnostics aimed at rationalising antimicrobial treatment of bacterial and fungal infection, particularly those caused by antimicrobial-resistant pathogens of clinical importance. Tests allowing rapid detection of drug susceptibility are particularly important to support rational clinical decision-making, leading to a more targeted and sustainable use of antimicrobials in One Health settings.

Introduction

A diagnostic is used to provide information about and to prevent or treat a disease. A radical change in the way antibiotics and antifungals are used is necessary since it is estimated that antibiotics and antifungals (in invasive infections) are 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 largely results from physicians and other antimicrobial prescribers being unable to make a precise diagnosis of infections in real-time. Unless rapid and affordable diagnostics are developed and are accessible for use for detection of bacterial/fungal infections and antimicrobial susceptibility testing, physicians and veterinarians will continue to prescribe antimicrobials empirically in any case in which they suspect an infection requiring treatment. Diagnosis of fungal infection is particularly problematic with few, if any, diagnostics available to aid the timely prescription of antifungals and appropriate use in the clinical and agricultural settings.

As the overall volume of antibacterial and antifungal use is associated with drug resistance, the development and use of rapid and cost-effective diagnostics to detect bacterial and fungal infections and antimicrobial susceptibility would reduce 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 speciation and detection of antimicrobial susceptibility. Special attention should be directed towards the development of diagnostics that can be used for detection of infections and 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 them before an appropriate antimicrobial drug can be prescribed and used. The effect of the wide-scale introduction of rapid diagnostics on minimising the emergence and spread of AMR needs to be quantified and justified with respect to human and animal health, and the cost associated with diagnostic use. The success of novel diagnostics will also depend on using appropriate reimbursement mechanisms and non-financial incentives. Cultural, contextual and behavioural determinants influence antimicrobial use and may determine which technologies and methods are most cost-effective and/or can be successfully implemented in resource-poor settings. The cost of a diagnostic 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 livestock production, and the limited diffusion of insurance policies that cover diagnostic costs for companion animals.

Companion diagnostics will facilitate antimicrobial development, particularly of narrow spectrum antibiotics and antifungals, by reducing the cost of clinical trials and enabling focused enrolment of patients infected with the targeted pathogens. Ideally, (companion) diagnostics would accompany the

development and approval of new antimicrobials to delay the development of resistance to these compounds and to enable their use within the scope of personalised medicine.

Rapid and inexpensive tests to guide antimicrobial prescription by veterinarians are urgently needed since the therapeutic options that are available for animals are very limited due to the bans and restrictions to reduce veterinary use of critically important antimicrobials combined with the historical lack of new veterinary drugs. Thus, the risk of prescribing a drug that is ineffective against the target pathogen is higher compared to human medicine, with negative consequences on animal health and welfare. For food-producing animals, the rapid and early detection of sick animals in the herd is important to allow individual treatment. Innovative approaches based on artificial intelligence are needed for identifying new diagnostic or prognostic markers and for developing early warning systems that allow detection of human or animal individuals predisposed to infection. Technologically, the tests for veterinary applications should 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 antimicrobial-resistant organisms, thereby increasing food safety. Within the One Health context, the topic of diagnostics should also involve new methods for detecting AMR in the environment, including in agriculture and aquaculture.

Novel technologies have already been developed to identify microbial pathogens and AMR, and if used effectively, many of these technologies could aid antimicrobial prescription and use. Although implementation of these new technologies has the potential to improve infection outcome, they typically increase costs of care since innovators often focus more on the 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 human and individualized veterinary medicine, will increase, rather than lower costs associated with diagnostics. Consequently, if these new technologies are to be successfully implemented in the future, new smarter and cost-effective applications are needed.

The successful introduction of early diagnostics in part depends on the awareness and empowerment of patients who can be provided with quality information and strategies to improve health literacy that would result in appropriate medicine taking behaviour. Health-literate patients have better health outcomes and higher quality of life, better awareness and knowledge about medicine use, and take greater responsibility for their own health. These patients are better at providing vital information and asking pertinent questions, which in the end promotes rational use of diagnostics and therapeutics. In the veterinary and agricultural sectors, educational efforts should be aimed at farmers and companion animal owners who need to understand the benefits of rapid testing in terms of both sustainable use of antimicrobials and a reduction in economic losses from disease among their animals and crops. Finally, significant differences exist between the needs of the high-income countries (HIC) and LMICs, and the recognition that strategies to approach the use of diagnostics will likely differ in different cultural and socio-economic settings.

Challenges

The challenges vary between sectors as they depend on the specific clinical and societal needs in each healthcare setting.

In livestock production, new diagnostics should meet the societal demand to minimize antimicrobial use and therefore are particularly needed to guide antimicrobial treatment of diseases that account for most antimicrobial consumption, namely enteric and respiratory diseases in pigs and cattle, and mastitis in dairy cows. Disease-specific interpretive criteria that take into consideration drug distribution in the intestinal tract are needed for antimicrobial susceptibility testing of enterotoxigenic *Escherichia coli* (ETEC), which has become virtually resistant all antimicrobials available for veterinary use following the restrictions in the use of colistin and zinc oxide. In companion animal medicine, antimicrobial choice is particularly difficult for managing common diseases caused by *E. coli* (e.g. urinary tract infections) and *Staphylococcus pseudintermedius* (e.g. deep pyoderma) since these pathogens are increasingly resistant to first line agents recommended by national and international guidelines, with levels of resistance exceeding 20% of clinical isolates from veterinary referral hospitals in certain geographical areas.

The development of rapid diagnostics requires secure funding for periods long enough to ensure their development from concept to production and assure implementation, ideally also 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 purchasers and to bring together disparate technologies into integrated simple systems at a reasonable cost. Another challenge is to identify real markets, where rapid (point-of-care) diagnostics in human and animal (both food-producing or companion) healthcare really matters enough to purchasers to drive demand and to encourage insurance companies or governments to pay for, or subsidise, their use.

A global platform to evaluate rapid diagnostics by aligning payers and providers, as well as engaging those who use and benefit from these rapid tests, would be beneficial in addressing AMR. The unique collections of clinical material and strains that have been gathered during the course of many funded projects in the EU and in JPIAMR member countries, and other regions as appropriate, should be made available for the development of these rapid tests. The selection of appropriate targets for detection and identification of pathogens and their resistance characteristics is critical.

Research and innovation objectives and activities

The overarching aim is to rationalise antimicrobial usage in One Health settings with a focus on three specific objectives.

1. Develop and evaluate new effective diagnostics and improve the efficacy of existing ones

Development of novel diagnostics and improvement of existing ones must be driven by needs in settings where the risk of antimicrobial misuse/overuse is higher or where the risk of treatment failure is higher due to AMR. Ultimately, new diagnostics should be affordable, rapid and suitable for LMICs and ideally point-of-care or point-of-need. Novel diagnostics should 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. 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 colonising or contaminating from organisms causing the 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.

Antimicrobial susceptibility testing (AST) interpretive criteria are needed for improving the clinical predictive value of AST since host-, species- and disease-specific interpretive criteria are lacking for important bacterial and fungal pathogens, especially in veterinary medicine.

Validated and standardized diagnostic methods for assessing quantitatively the efficacy of unconventional antimicrobials (e.g. phage or virulence inhibitors) and alternatives to antimicrobials (e.g. prebiotics and probiotics) would be useful to implement the use of these products in clinical practice across any sectors, thereby reducing antimicrobial use and AMR selective pressure.

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 DNAs, 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 by 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.

2. Evaluate field performance, feasibility and impact of diagnostics

Well-designed pre-clinical studies and clinical trials as well as farm 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. Adaptable research projects that respond to the outcomes of the evaluation studies will be needed to address these aspects. Research is needed to understand how robust the new diagnostic methods are. This will be an important parameter when deploying the diagnostic to the intended users.

Studies to evaluate and provide evidence for the benefit of using diagnostics are needed. These should consider 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 on 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 in fungal infections, 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

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. Despite the availability of antifungal susceptibility testing these tests are rarely adopted nor routinely performed, and an effort should be made to understand specific barriers for antifungal resistance detection and develop strategies for their implementation in the appropriate One Health settings. Barriers and facilitators to the acceptance and uptake of new diagnostics should be identified through an interdisciplinary approach combining wet and dry sciences. 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 economical 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 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 used of diagnostics, especially in view of the experiences during the COVID-19 pandemic.

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 optimize antimicrobial use.

Surveillance

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

The goal of this priority topic is to strengthen the research on surveillance systems, methods and protocols to optimise the surveillance of AMR and antimicrobial use (AMU) using a One Health approach. Optimisation of surveillance systems needs to consider existing global and local surveillance and research networks (Appendix 1).

Introduction

Surveillance is the continuous, systematic collection, analysis and interpretation of data needed for action, e.g. planning, implementation, and evaluation of interventions to mitigate antimicrobial resistance (AMR). Global and local surveillance of AMR and AMU is essential to monitor AMR trends and to guide and evaluate policy measures. AMR surveillance is needed for One Health policy purposes to understand the development, transmission and directionality of the spread of AMR and to estimate the nature and burden of AMR in global and local settings, and to guide policymakers on critical AMR mitigation measures. Surveillance serves as a warning system and strengthens the response to the emergence/escalation of AMR and the outbreak of drug-resistant bacteria and fungi in human and animal health, food systems, and the environment.

Ideally, a standardized AMR and AMU surveillance framework/protocol adopted by all countries would generate comparable data to mitigate AMR globally and locally. In addition, monitoring AMU would encourage countries to adopt regulations to control the use of antimicrobials in human and animal health, food systems, and the environment. The One Health approach in surveillance and infection prevention and control requires that all sectors are engaged. There are several global and regional surveillance systems in place (Appendix 1) and several countries undertake both AMR and AMU surveillance

Challenges

Existing national, regional and global surveillance systems do not meet all the needs and expectations of policymakers, clinicians, veterinary health professionals, public health workers, livestock and crop farming professionals and researchers. There is substantial heterogeneity across countries and regions that includes but are not limited to:

- quality of data library;
- samples source and sampling frame ;
- availability of microbiological diagnostics for accurate detection;
- harmonization of definitions, methods, and tools;
- selection of microorganisms, resistance phenotypes and determinants included;
- Lack of data of non-bacterial sentinel pathogens;
- quality of antimicrobial susceptibility testing
- availability and quality of national reporting systems;
- lack of data triangulation (between operational units of surveillance and also between information of microbes and hosts/environments)

Furthermore, these surveillance systems do not cover all components of One Health - most are directed at human and to a lesser extent veterinary health, with environmental surveillance of AMR, determinants and drivers of resistance in their infancy. Moreover, most systems report on microbial culture and susceptibility, and only a few surveillance systems undertake genomic surveillance or link AMR data with epidemiology or outcome. Surveillance occurs in silos, with minimal integration and triangulation of data across sectors and countries. A challenge for future efficient and purposeful AMR surveillance is to define standards for certain components (e.g. targets, metadata, and detection and typing methods) as well as the minimal information on samples required for their use in clinical, epidemiological and ecological surveillance, research and development across all One Health sectors. Moreover, characteristics for early warning systems and risk assessment tools need to be defined. The fitness of purpose and the fitness for purpose of existing national, regional and global AMR and AMU surveillance systems should thus be revisited.

The use (and misuse) of antimicrobials is a major driver for the emergence and escalation of AMR. It is therefore of utmost importance to correlate AMR data with data on antibiotic and antifungal use to understand drivers of AMR in different One Health settings and assess the efficacy of antimicrobial stewardship interventions. The methods, study design and sampling frame strategies for surveillance of the use of antibiotics and antifungals in human and veterinary medicine (including livestock and companion animals), and crop farming needs to be strengthened.

Globalisation, manifested by the increase in human travelling (including medical tourism), and the international trade of animals, foods and goods, changing migration patterns and climate change will influence how AMR emerges and spreads around the world. Existing surveillance systems, listed in appendix 1, could be used as blueprints, which could be extended in terms of global coverage, complimentary genomic surveillance, epidemiology and treatment outcome. Extending surveillance to reflect social processes (climate or conflict/war refugees, migrants, travellers), environmental dimensions, and hotspots and key reservoirs for transmission is also needed. While striving to integrate or harmonise new types of information with existing surveillance protocols and systems, these efforts need to be done with consideration for the different needs and capacities between sectors. An example of an integrated One Health surveillance network coordinated by the WHO AGISAR group is the Tricycle project[8].

Surveillance needs to be extended to antifungal resistance, which is in its infancy. International surveillance systems rarely monitor antifungal resistance or antifungal use. *Candida auris* has been described as the cause of outbreaks that are difficult to control and eradicate with pan-resistant isolates detected in clinical samples. Azole resistance in *Aspergillus fumigatus* is a rising threat linked to the presence of azoles in the environment used to prevent fungal infections in crops. The only international program in which fungal infections are included is the SENTRY[9] , which is a private initiative with several limitations. The number of antifungals available in the clinical setting is very limited, especially in LMICs where several essential antifungals are not available . The Global Action on Fungal Infections has provided maps showing availability of key antifungal medicines in each country[10]. Further investigation of the antifungal usage, particularly in agricultural settings, is needed on a global scale.

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

[9] https://www.jmilabs.com/sentry-surveillance-program/

[10] *https://www.gaffi.org/antifungal-drug-maps/*

The main needs in antifungal resistance surveillance are to improve methods and increase laboratory capacity, especially in LMICs. CLSI and EUCAST[11] have reference microdilution methods, but these are cumbersome and not suitable for many clinical laboratories. The correlation between the results obtained with commercial methods used in clinical laboratories and reference methods depends on the fungal species and antifungal agent, and are not optimized. In many LMICs antifungal susceptibility-testing is not performed or very restricted to reference laboratories.

An early warning system at the global and local level is needed to inform timeous mitigation strategies (e.g. antimicrobial stewardship, IPC and WASH measures). Preferably, such a global warning system on AMR should be integrated within existing (inter)national early warning systems on infectious diseases, like the Early Warning and Response System for communicable diseases in the EU/EEA (EWRS)[12], Joint FAO/OIE/WHO Global Early Warning System (GLEWS)[13], Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)[14] and others. For releasing alerts and initiating appropriate responses, warning systems rely on grading of hazards indicated by collated data. There is currently a substantial lack of knowledge of the mechanisms triggered by already identified or yet to-be disclosed drivers of AMR spread within and across sectors. This hampers the modelling of developments and the definition of sensible control points, as well as of (molecular) markers for microbial risk assessment to be monitored at the control points.

Research and innovation objectives and activities

Improve and standardise/harmonize AMR surveillance systems, from sampling to data analysis and use for action.

The needs of different stakeholders regarding AMR and AMU surveillance data must be thoroughly explored to ensure that surveillance systems show fitness of purpose and fitness for purpose. Surveillance systems should generate accurate, real-time, quality assured surveillance data for stakeholder action (ideally, on-line and real-time data). Guidance on the methodology and best practices for the standardisation/harmonization of AMR and AMU surveillance systems to allow for comparison of results across countries, regions and globally is imperative. Alignment can be achieved by establishing standardized/harmonized protocols at laboratory level or by cross-compatible methods such as establishing tailored sampling schemes for different sectors which collate supplementary data from different fields. Currently, limited surveillance systems exist in the antifungals area, GLASS program is considering the inclusion of Candida and healthcare availability of antifungals is being monitored by GAFFI. Therefore, surveillance data on antifungals including AMU is urgently needed globally.

Specific objectives for research and innovation are to define the components of an inter-coordinated One Health surveillance protocol that includes a minimum sampling framework, powered sample size, ideal sample sources, sampling frequency, standard operating procedures for sampling and quality-controlled laboratory investigations and integrated and triangulated analysis of AMR and AMU data. Development of clinical and/or ecological breakpoints for bacteria and fungi from non-human sources is integral to this. Alignment of and access to surveillance frameworks and platforms between high-income countries (HICs) and low- and middle-income countries (LMICs) and within public and private sectors should be addressed. A minimum phenotypic and genomic surveillance framework and a

[11] https://community.clsi.org/about/blog/ast-news-update-2019-practical-tips-2/

[12] *https://ewrs.ecdc.europa.eu/*

[13] *http://www.glews.net/*

[14] *https://www.glopid-r.org/*

platform including whole genome sequencing (WGS) should be explored for LMICs. Technical development needs to be paired with descriptions of the value of monitoring AMR and AMU, for sustainable stakeholder engagement and funding.

Collaborative efforts between private and public sectors would facilitate for success in achieving these goals. Furthermore, studies should focus on substandard and falsified (SF) antimicrobials as well as the supply chains and delivery routes. This knowledge should aid action against this possibly underestimated aspect of the antibiotic and antifungal consumption and subsequent resistance in certain countries.

Strengthen the use of surveillance data to identify reservoirs of AMR in the three sectors and enable risk assessment

The role of different reservoirs of AMR, and their impact on human, animal, crop and environmental health, need to be better understood for the purpose of risk assessment and reduction of AMR.

Studies are needed on AMR at One Health interfaces to determine the types of surveillance that can generate data to illustrate transmission dynamics for risk assessment and management. The relative contribution of selective pressure and transmission in different settings needs to be better understood, and it is important to identify sensible control points (hotspots) to build up resource-efficient surveillance systems. Scientific evidence should be used to create political and public awareness of the importance of managing and limiting the spread of AMR and optimising AMU, within and between One Health sectors.

Structured surveys and surveillance of the environmental dimensions of AMR should be harmonised by coherent sampling frames and a comparable data structure. Novel technologies that allow accurate detection and prediction of the prevalence and diversity of resistance genes, including co-selected AMR determinants and associated mobile genetic elements comprising the resistome and mobilome respectively, should be further developed. Methods for monitoring the prevalence and dynamics of AMR in many different, relevant environments need to be developed, as well as operational units of surveillance that can monitor the dynamics of AMR, time and changes in climate and social processes.

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

Efforts are required to design surveillance data library, analysis and interpretation, especially in LMICs, to assess the impact of interventions and the impact of AMR on One Health (burden, transmission, and emergence). Microbiological information should thus be linked to clinical and epidemiological data (e.g. information gathered for diagnostic purposes), patient outcome and characteristics, and to similar data from the animal, agricultural and environmental sectors. Including genetic markers for identification of transmission and outbreaks would support investigation of the spread of AMR within and between settings. The development of on-line, real-time or automated analysis, could also strengthen surveillance by optimizing the use of available data. Here, innovation and methodological development may need to include expertise in digitalization, information technology and similar fields.

Interactive, updated and user-friendly websites, mobile applications and the use of social networks giving rapid access to AMR and AMU surveillance data will provide to professionals of the three sectors and antimicrobial users with access to information that supports improved decision-making.

Increased understanding of the estimations of the real burden (in terms of infection, death, cost etc.) associated with AMR worldwide is needed, especially in LMICs where there is a large knowledge gap. These issues need to be addressed with an interdisciplinary approach, e.g. in collaboration between natural and social sciences. Moreover, agricultural and environmental surveillance for antibiotics and antifungals residues and resistance genes in sewage, water systems, food and agricultural wastes could provide data on antibiotic and antifungal use in humans, animals and farming systems, in the absence of conventional surveillance (as shown in Global Sewage Project[15]). Further research is required to generate innovative tools for rapid detection of antimicrobial resistance genes and mobile genetic elements using metagenomics and how they can be efficiently utilized to monitor the global spread of AMR.

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

Research infrastructures should be established or further developed in a coordinated fashion to facilitate the integration of surveillance data to perform (inter)national meta-data analysis. There is a need to create, maintain or coordinate open access data warehouses where phenotypic and genomic surveillance data can be imported, quality checked, and individual isolates can be put into a global context (for instance by improving bioinformatics pipelines). The difficulties to implement open tools for data sharing due to law regulations in different countries should also be considered. Research on novel technologies should determine whether conventional surveillance approaches based on phenotypic characterization of isolates should be replaced or complemented by genomic surveillance. Data on AMR and AMU surveillance should be linked with information on colonization, (co-)infection and host factors (such as clinically available information) where appropriate.

Lastly, new technology and research infrastructures on AMR surveillance require capacity building to provide . Hands-on, practical training on the analysis and interpretation of AMR data, and encourage different stakeholders to reconfigure their workplace to facilitate the incorporation of surveillance data.

Appendix 1 : Major international surveillance networks and systems.

Table 1: Examples of Major international surveillance networks and systems.

Host	Acronym	Name	Description
European Centre for Disease Prevention and Control (ECDC)	EARS-Net	European Antimicrobial Resistance Surveillance Network	Europe-wide network of national surveillance systems of AMR for seven bacterial pathogens causing invasive infections in humans.
World Health Organization (WHO)	CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance	Network of national AMR surveillance systems including all countries of the WHO European Region that are not part of EARS-Net.
European Centre for Disease Prevention and Control (ECDC)	ESAC-Net	European Surveillance of Antibiotic Consumption Network	Europe-wide network of national surveillance systems, providing European reference data on

[15] *https://www.compare-europe.eu/Library/Global-Sewage-Surveillance-Project*

Host	Acronym	Name	Description
			antimicrobial consumption, both in the community and in the hospital sector.
European Centre for Disease Prevention and Control (ECDC)	HAI-Net	European Healthcare Associated Infections Network	Europe-wide network, coordinating point prevalence survey of HAI and antimicrobial use in acute care hospitals, surveillance of surgical site infections, surveillance of HAI in intensive care units and the repeated prevalence surveys of HAI and antimicrobial use in long-term care facilities.
European Centre for Disease Prevention and Control (ECDC)	FWD-NET	European Food- and Waterborne Diseases and Zoonoses	Surveillance on 21 human diseases acquired through consumption of food or water, or through contact with animals. Parasitic and viral agents are included. AMR data are collected for *Salmonella*, *Campylobacter*, and *E. coli*.
European Medicine Agency (EMA)	ESVAC	European Surveillance of Veterinary Antimicrobial Consumption	Europe-wide network (30 countries) which collects standardised **data on the sales of antimicrobial drugs** in animals in EU/EEA.
European Food Safety Authority (EFSA)		Network on Antimicrobial Resistance Data Reporting	European network (31 countries) collecting harmonised data on antimicrobial resistance in zoonotic and indicator bacteria from food-producing animals and food in EU/EEA.
World Health Organization (WHO)	GLASS	Global Antimicrobial Resistance Surveillance System http://www.who.int/glass/en/	The first global system to incorporate official national data from surveillance of AMR & AMU, with a standardized approach to the collection, analysis, and sharing of AMR, AMC and AMU data. It follows a One Health model for AMR surveillance and targets human bacterial pathogens considered the greatest threat globally (124 countries and territories included). A pilot testing phase for the inclusion of fungal surveillance data into GLASS (with an initial focus on bloodstream Candida infections) took place during 2021-2022, with national-level implementation planned for 2023
WHO AGISAR	Tricycle	One Health Surveillance	Monitoring of ESBL-*E. coli* in humans (carriage and infections), the food-chain and the environment.

Host	Acronym	Name	Description
Asia Pacific Foundation for Infectious Diseases	ANSORP	Asian Network for Surveillance of Resistant Pathogens	International research group for antimicrobial researchers in the Asian region - consists of over 230 investigators and 123 centres in 14 countries in Asia and the Middle East.
MSD	SMART	Study for Monitoring Antimicrobial Resistance Trends	Monitoring the in vitro susceptibility of clinical bacterial isolates to antimicrobials in intra-abdominal infections worldwide
GSK	SOAR	Survey of antibiotic resistance	Collection of antibiotic surveillance data on the susceptibility of pathogens that cause community-acquired infections in countries where resistance data can be scarce.
Pfizer	ATLAS	Antimicrobial Testing Leadership And Surveillance	Interactive website that provides global AMR surveillance data from 60 countries. Integrates three surveillance programs (TEST: Tigecycline Evaluation and Surveillance Trial, AWARE: Assessing Worldwide Antimicrobial Resistance Evaluation, and INFORM: International Network for Optimal Resistance Monitoring). Generated global bacterial susceptibility data versus a panel of antibiotics from 760 sites in 73 countries.
Wellcome Trust, UK	SEDRIC	Surveillance and Epidemiology of Drug-resistant Infections Consortium	Network of 12 international experts to share expertise and act to tackle the gaps in AMR surveillance and epidemiology, develop guidelines and tools to encourage data sharing, translate scientific evidence into policy.
COMBACTE-Magnet	EPI-Net	Surveillance platform of antimicrobial resistance including human and animal data	Network of surveillance systems, experts and stakeholders collecting resistance data on the WHO priority pathogens for R&D of new antibiotics.
Global Action for Fungal Infections	GAFFI	Registration, availability and price of antifungal agents in each country https://www.gaffi.org/antifungal-drug-maps/	GAFFI presents fungal disease burden estimates for > 80 countries,, fungal disease fact sheets, brief policy statements and clinical availability of antifungals.

Table 2: Important related links

Reference	Link
GLASS	http://www.who.int/glass/en/
EARS-NET	https://ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-a laboratory-networks/ears-net
CAESAR	http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/about-amr/central-asian-and-eastern-european-surveillance-of-antimicrobial-resistance-caesar
GAFFI	https://www.gaffi.org/antifungal-drug-maps/
EMA jiacra-reports	https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/analysis-antimicrobial-consumption-resistance-jiacra-reports

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Transmission & Evolution

Understanding and preventing 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 key to find 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. Other measures than 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 knowledge about their recent origin is limited. The environmental niches, the relative roles of different drivers, and the genetic processes involved in their emergence and establishment 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 studied than for antibiotic resistance. Horizontal acquisition of resistance factors as well as resistance causing mutations in existing DNA both drive antimicrobial resistance evolution via adaptive processes. These include e.g. 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 colonization 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 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 recognized 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 colonization 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. Dependent 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 fecal 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.

Challenges

This research priority aims to improve our understanding of the complexity of how resistance develops and spread 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, economy, 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 endeavour 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 infection load, 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 and activities

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 mitigations, research is needed on the fundamental evolutionary processes and the detailed mechanisms, mobilizing 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 characterise 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 generalizations 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 favour mobilization 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, feces) 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.

Understand the directionality and scale of transmission of resistant microorganisms within and between human and animal populations, and identify critical transmission routes and underlying drivers

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. Methods that can better utilize 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 recognize 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 within and between humans, animals and the environment needs to be better characterized. Bioavailability, competition with other microorganisms, and variable abiotic factors and selection pressures may strongly influence their effect. 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 regards to the transfer back to humans. Studies that characterize 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 back 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 lack of sanitation and effective hygiene measures is likely to greatly influence risks. Social factors underlying the (lack of) transmission control may be 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.

Identify, design and evaluate technical and social interventions to control emergence and transmission of resistance, based e.g. 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. 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 prioritizing interventions need to weigh in technical, geographical, economic, social, ethical and political concerns. 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 recognized driver of AMR, research aimed at optimizing the use of antimicrobials is key. 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 human, 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 optimizing 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. 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. This includes both technical, economical, 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. It should, for example, be investigated which sanitary measures are need for manure used for fertilization 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 optimized to reduce the burden of antibiotic residues and of AMR determinants.

On the exposure side, we need more knowledge on interventions that prevent colonization, 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 leads 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 account externalities).

Prevention and Interventions

Improving interventions to reduce burden of infectious diseases, rationalise antibiotic use and increase systemic capacity to mitigate Antimicrobial Resistance (AMR) in One Health settings

The goal of this topic is to define key research priorities to reduce the emergence and spread of AMR in a one-health setting using intervention and implementation research. In this context, interventions refer to all strategies, tools, programmes and actions that prevent or reduce the incidence and dissemination of infections, and specifically drug-resistant infections, by infection prevention and control, the promotion of responsible antimicrobial use (AMU), health systems strengthening, promotion of vaccine uptake, community engagement for rational antibiotic use, sustainable agricultural practices, prevention of environmental contamination with antimicrobials from various sources and public health measures such as water, sanitation and hygiene (WASH).

As reinforced by the Covid-19 pandemic, AMR prevention and interventions can fail unless its addressed on a global and systemic scale. Interventions should especially consider challenges in low-resource contexts, ensure cost-effectiveness and involve relevant stakeholders.

Introduction

The Research and Development (R&D) pipeline for antimicrobials have been drying up in the last few decades, with very few novel antimicrobials being commercialised. This is compounded by increasing resistance to existing antimicrobials, which are accessible and stewarded with different levels of effectiveness globally. In order to prolong the usefulness of existing and new antimicrobials, effective and validated interventions should be implemented for infectious disease management and appropriate antimicrobial use in clinical and veterinary medicine, agriculture, aquaculture, and food production. Adoption of a One Health approach is essential for improved understanding of the acquisition, evolution and transmission pathways of AMR, and to develop effective interventions. The importance of implementation research in addressing the emergence and spread of AMR has been highlighted in landmark documents like the report of the Inter-Agency Coordination Group (IACG-AMR). However, efforts to pilot innovative interventions and strategizing for scale-up of successful interventions have been limited. Uptake of evidence-based AMR mitigation strategies and the use of technological innovations is also slow due to socio-economic and behavioural determinants. Therefore, strategies to address these barriers need to be equally diverse and adapted in all One Health settings.

Several recent reports on AMR have highlighted the importance of political, socio-behavioural, and technological interventions for improving the health and wellbeing of populations. The intervention design should be cognizant about the expectations of the target stakeholder groups and align well with the priorities of communities and countries. These interventions are viewed as crucial for healthier people and animals, as well as to mitigate the spread of

AMR in humans, animals and the environment. Special emphasis should also be placed on sustainable change in behaviour among the targets of the intervention, with increased systemic capacity to address AMR.

Implementation research is defined as 'the scientific inquiry into questions concerning implementation – the act of carrying an intention into effect, which in health research can be policies, programmes, or individual practices, which are collectively called interventions.' (Peters DH et al, 2013) Implementation research is essential for translating evidence to policy; and for informing strategies for scale-up of a particular intervention. The feasibility and sustainability of interventions are evaluated through implementation research, in addition to looking at drivers of behaviour change. In most cases, it will be accompanied by some economic evaluation method which can generate data on the cost-effectiveness of the intervention. Ultimately, this research will contribute to the prevention of drug-resistant infections, improved quality of human and animal healthcare, improved patient safety and biosecurity, and global environmental protection.

Challenges

There are many challenges spanning across One Health settings affecting AMR prevention and interventions. For example, there have been numerous campaigns to promote the prudent use of antimicrobials, varying from simple, low-cost internet campaigns to expensive mass-media efforts. The capacity of individual campaigns to affect and sustain effective behavioural change and influence the development of resistance to antimicrobials is difficult to assess. Further research is needed, particularly in low-resource settings, to quantify the impact of information, training and public awareness campaigns on the emergence, spread, knowledge, practices, and public perception of AMR and AMU. In addition, we still do not have sufficient insights on the utility of various behaviour change theories and community engagement models in delivering AMR interventions.

Suboptimal investment in health systems strengthening has been a challenge in most parts of the world and these systemic insufficiencies were evident during the Covid19 pandemic. Healthcare systems in low-resource settings are in dire need of improved technologies for diagnosing and treating infectious diseases. There are human resource limitations affecting the quality of care, especially with regard to the treatment of infectious diseases. Adapted preventive measures and interventions to reduce the emergence and transmission of AMR, as well as access to the appropriate antibiotics and antifungals for treatment of infections is equally important.

The need to introduce new evidence-based interventions is essential in veterinary medicine and farming, which has few prospects for the introduction of treatment options based on new antimicrobials. New farming and production methods, crop treatment and interventions to improve biosecurity in livestock production may prevent infectious diseases and reduce the need for antimicrobial use without threatening food production or profitability. The successful introduction of interventions depends on complex relations between awareness and acceptance by producers, prescribers and consumers, use of financial incentives, introduction of regulation, production yield, animal health and welfare, and development of resistance

affecting human health. More research is needed to identify appropriate and efficient approaches to implement antimicrobial stewardship or benchmarking, in countries with diverse agricultural production systems and livestock populations. Lack of access to appropriate diagnostics, human resource constraints, unregulated access to antimicrobials and poor prescribing competencies are also major challenges in food animal production. Besides, antimicrobial use in horticulture and plant health is often hidden and mislabelled, thereby hampering interventions to rationalise antimicrobial misuse in agriculture.

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

Research and innovation objectives and activities

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

Novel and innovative interventions are needed to better detect, prevent, and control the spread of AMR. This should complement the efforts to identify existing evidence-based interventions that are appropriate for scale-up. A global and systemic approach, taking into account the interests of Low and Middle Income Countries (LMICs) too, is needed to identify the most appropriate interventions for the particular country's context. Since AMR is closely linked to pandemic preparedness and health security, the learnings from Covid19 should also be used to design interventions which can contain the issue. Innovative interventions may include decision support software to increase quality of prescriptions, more efficient diagnostic platforms to identify infectious conditions, novel AMR surveillance strategies like sewage monitoring and nanoparticle based materials to tackle biofilm associated infections. Innovation can also be in communication or modifying market signals, with novel techniques to influence the decision-making of target stakeholder groups.

Piloting strategies for measuring the AMR co-benefits of existing public health interventions such as vaccines, IPC, WASH and Universal Health Coverage taking a One Health approach

There are several healthcare delivery and animal health interventions which can influence the AMR. These AMR-sensitive interventions are not accounted for, when we consider implementing action plans or roadmaps to contain AMR. Therefore, we need to co-opt many of these existing activities and programmes into AMR action. This includes having models for measuring (qualitative or quantitative) change in the burden of AMR, models for undertaking

such studies at various levels and bringing an AMR lens to existing public health interventions through training, data collection systems and IR.

Evaluating the policy, economic, social and technical implications of AMR prevention and control interventions to increase uptake and acceptance in One Health settings

Uptake and acceptance of prevention and control interventions in One Health settings need to be analysed with respect to its policy, economic, social and technical aspects. The interventions should be evaluated for cost-effectiveness, technical & administrative feasibility from a societal perspective and acceptability in the socio-cultural settings. In addition, well-designed multicentre prospective intervention trials are essential to establish the effectiveness of AMR infection prevention and control strategies. Interventions should be considered for such an evaluation to generate good quality, localised evidence to inform scale-up.

Strategies to involve target stakeholder groups in co-designing and owning interventions to prevent and control the spread of AMR

Drivers and barriers to behavioural change need to be studied to inform the interventions to increase awareness and perception of AMR and AMU among producers, prescribers, users, and consumers. Ownership by all stakeholders in the value chain is essential to increase the impact of the intervention necessitating the inclusion of all stakeholders from inception. Robust involvement of communities through community engagement strategies and use of behavioural change models for influencing the decisions of target stakeholder groups should be a priority- and this calls for social and behavioural science expertise while designing interventions. Population based studies to assess the quality and effects of implementation strategies on promoting the prudent use of antimicrobials in various settings and countries are required. It is also important to understand better why previous implementation strategies have failed to be effective. This too requires an implementation research/science framework.

Incorporating equity and regulatory strengthening into the interventions to prevent and control AMR

Evolution and spread of AMR is linked to the issue of appropriate access to effective treatments for communicable diseases in human and animal health. AMR also has a proven interface with issues like access to WASH, gender and climate change. Therefore, applying an equity lens while designing interventions to contain AMR is essential. Developing various models for increasing access to newer antibiotics and strategies to encourage diagnostic stewardship in public health systems must be built into the roll out of Universal Health Coverage especially in LMICs. Innovative techniques for increasing cost-effectiveness of WASH in low-resource settings and quantifying the impact of climate change on AMR can also be considered. The regulatory ecosystem in the countries and financing available for AMR interventions affect the evolution and transmission of AMR. Research into strategies to strengthen regulatory systems, innovative financing models for implementing AMR actions, piloting AMR specific smart regulations and optimizing regulatory compliance should be a

priority. All the relevant stakeholders should be involved in the development and implementation of policies and strategies to strengthen a country's capacity to implement regulations should be researched. There are obvious regulatory gaps affecting AMR action in many situations- from lack of globally accepted standards for antibiotic residues in waste water to universal guidelines for certifying antibiotic-smart food products.

Strategies to increase the impact of educational campaigns to increase awareness about antimicrobial resistance and prudent use of antibiotics

Educational campaigns and training programmes to promote the prudent use of antibiotics and antifungals is a key intervention measure to enhance stewardship. It is important to raise the awareness of the burden of AMR among all sections of the society, including policymakers. Campaigns may apply multiple simultaneous interventions making it difficult to establish which strategy is most efficient in changing attitudes, beliefs, norms, and practices. Further research should assess the impact of information, training, and public campaigns on the development of resistance to antimicrobials, resource allocation for AMR specific activities and the general public awareness of the AMR issue over time, particularly in low-resource settings. The effectiveness of various messaging frames, messaging & reinforcement strategies and modes of transmitting the messages to the general public should be evaluated before investing in public campaigns on AMR.