The need for One Health systems-thinking approaches to understand multiscale dissemination of antimicrobial resistance

Kathryn E Arnold, Gabrielle Laing, Barry J McMahon, Séamus Fanning, Dov J Stekel, Ole Pahl, Lucy Coyne, Sophia M Latham, K Marie McIntyre

Although the effects of antimicrobial resistance (AMR) are most obvious at clinical treatment failure, AMR evolution, transmission, and dispersal happen largely in environmental settings, for example within farms, waterways, livestock, and wildlife. We argue that systems-thinking, One Health approaches are crucial for tackling AMR, by understanding and predicting how anthropogenic activities interact within environmental subsystems, to drive AMR emergence and transmission. Innovative computational methods integrating big data streams (eg, from clinical, agricultural, and environmental monitoring) will accelerate our understanding of AMR, supporting decision making. There are challenges to accessing, integrating, synthesising, and interpreting such complex, multidimensional, heterogeneous datasets, including the lack of specific metrics to quantify anthropogenic AMR. Moreover, data confidentiality, geopolitical and cultural variation, surveillance gaps, and science funding cause biases, uncertainty, and gaps in AMR data and metadata. Combining systems-thinking with modelling will allow exploration, scaling-up, and extrapolation of existing data. This combination will provide vital understanding of the dynamic movement and transmission of AMR within and among environmental subsystems, and its effects across the greater system. Consequently, strategies for slowing down AMR dissemination can be modelled and compared for efficacy and cost-effectiveness.

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Department of Environment and Geography, University of York, York, UK (Prof K E Arnold PhD)**; Unlimit Health, London, UK** (G Laing PhD)**; UCD School of Agriculture and Food Science** (B J McMahon PhD)**, UCD-Centre for Food Safety, School of Public Health, Physiotherapy & Sports Science, University College Dublin, Dublin, Ireland** (Prof S Fanning DSc)**; School of Biosciences, University of Nottingham, Sutton Bonington Campus, Loughborough, UK** (Prof D J Stekel PhD)**; Department of Mathematics and Applied Mathematics, University of Johannesburg, Johannesburg, South Africa** (Prof D J Stekel)**; Department of Civil Engineering and Environmental Management, School of Computing, Engineering and Built Environment, Glasgow Caledonian University, Glasgow, UK** (Prof O Pahl PhD)**; Department of Livestock and One Health, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK** (L Coyne PhD, S M Latham PhD, K M McIntyre PhD)**; National Office of Animal Health, Stevenage, UK** (L Coyne)**; Modelling, Evidence and Policy group, School of Natural and Environmental Sciences, Newcastle University, Newcastle, UK** (K M McIntyre)

Correspondence to:
Kathryn E Arnold, Department of Environment and Geography, University of York, York YO10 5DD, UK
Kathryn.Arnold@york.ac.uk

Introduction

Antimicrobial resistance (AMR) remains one of the most complex and pressing challenges for society which, because of the COVID-19 pandemic, now needs addressing within changing health-care, economic, and social landscapes.[1] Evolution of resistance and subsequent transmission of resistance genes is not restricted to clinical settings or human-to-human transfer within the community. Instead, uncontrolled or insufficiently treated waste releases from humans and agriculture along with environmental factors, such as wildlife migration, agrochemical use, and heavy metals in soils and flows of surface waters, almost certainly contribute to globally increasing AMR levels in all domains of the One Health paradigm.[2] Here, we use the term AMR, rather than antibiotic resistance, because bacteria and other microbes, particularly in the natural environment, can develop resistance following exposure to substances that are not specifically antibacterial or antibiotic (eg, metals and detergents). Debate continues regarding the key drivers and pathways of AMR evolution and dissemination.[3] Important but underappreciated components of the AMR system include the natural environment, which underpins the health and sustainability of human, animal (including both livestock and wildlife), and plant populations.[4] Despite increasing recognition of the natural environment acting as humankind's main resilience buffer (with anthropogenic infrastructure and human wellbeing sitting inside this), these components are overlooked (figure 1).

When studying infectious diseases including AMR, there is a tendency to focus on solving individual elements of the problem, such as reducing antimicrobial usage, improving diagnostics, or developing new antimicrobial drugs and vaccines. Such a standpoint (ie, finding mechanisms to reduce specific hazards) creates a narrowed view of this societal challenge. Increasingly, dynamic perspectives that explore how issues within subsystems (eg, the separate human, animal, and environmental dimensions) influence one another within a complete system require so-called "systems-thinking

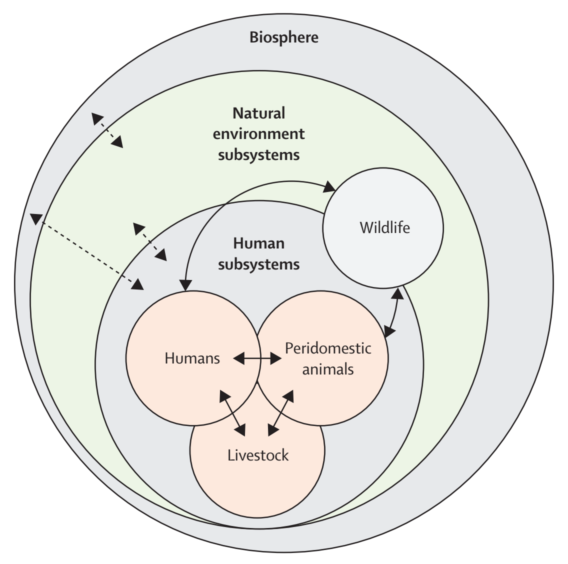

Figure 1: **A One Health paradigm, systems-thinking approach describing evolution and dissemination of antimicrobial resistance**
Solid arrows show the well studied flow of antimicrobial resistance (AMR) among humans and other animals. Dashed arrows depict movement of AMR among different environmental subsystems, which to date have been less well studied. The development of resistance is mediated by biological, physical, chemical, and human-mediated processes and interactions between these, which we suggest should be studied using a One Health systems-thinking approach that encompasses animal and human hosts within the natural environment including wildlife, all of which function within the greater biosphere system.

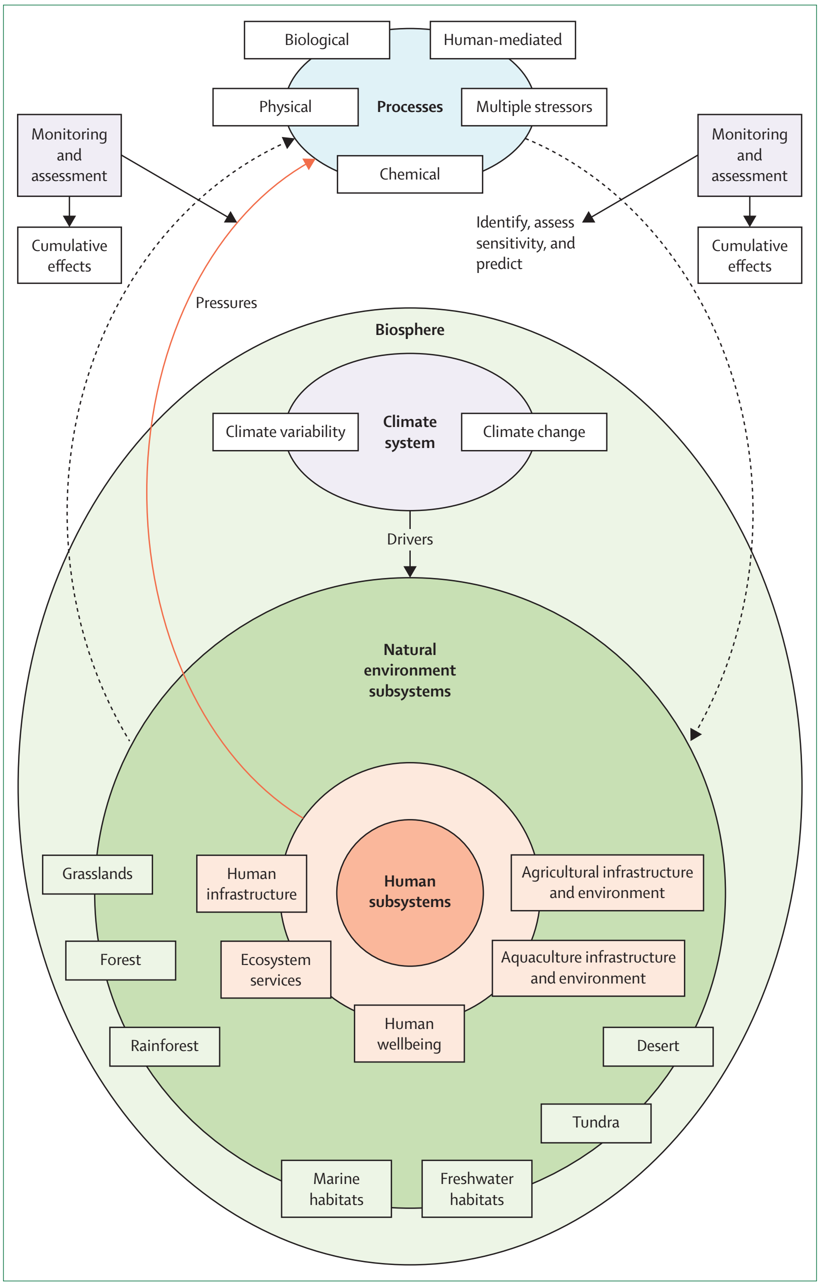

Figure 2: **The AMR social-ecological-environmental system**
The linkages between the development of antimicrobial resistance (AMR), the human subsystem, climate forcing, responses in the natural environment subsystem (at multiple trophic levels and spatial scales), and functional processes between all these subsystems and systems. Dashed black arrows show the effects of functional processes on the subsystems in which AMR develops and is transmitted, and vice versa. Human subsystems apply extra pressures (red arrow) on functional processes. Adapted from a figure by Bograd and colleagues (2019).[24]

approaches”.[5,6] Such approaches need to use and understand multisectoral information using multidisciplinary, interdisciplinary, and trans-disciplinary methods to inform outputs describing a spectrum of possible outcomes.[7] In this Personal View, we propose a theoretical framework for developing systems-thinking approaches to AMR, based on the One Health concept.[8,9]

Systems-thinking approaches allow for the systematic collation and synthesis of disparate data sources, such as quantitative data, expert knowledge, and stakeholders’ understanding. Moreover, a systems approach can involve designing and evaluating a systems intervention so that subsystems operating within the system are also considered.[10] A systems approach is undertaken by inclusively involving stakeholders and disparate data sources, to create a conceptual pathway of interactions between dynamic subsystems that allows for understanding causal chains, and how changes will affect the full system. With this approach, interventions can be explored taking into consideration the amplifying elements and feedback loops, and previously unidentified synergies across the subsystems.[10] For example, we would potentially be able to unpick transmission of antimicrobial-resistant bacteria and mobile genetic elements (MGEs), plus observe the development of antimicrobial resistant genes (ARGs). A systems-thinking approach will facilitate the development and evaluation of interventions against emerging resistance problems.[11–13]

Here, we make the case that taking such systems-thinking approaches within a One Health framework[14] should involve innovative computational approaches designed to integrate complex and heterogeneous data streams (eg, from clinical, agricultural, and environmental monitoring) into an ontology including multidimensional data resources. Therefore, we can start addressing the identified knowledge gaps including the relative contributions of different sources to development of resistance and the role of the environment, particularly anthropogenic inputs into resistance development. Such big data analyses can both accelerate our understanding of AMR, and importantly, support decision making given the complexity and heterogeneity of the systems.[15]

Evidence for a role of the environment in AMR

A systems-thinking, One Health framework for understanding AMR will help investigate predictions that the environment is (1) an important source of AMR, (2) an important reservoir of AMR, (3) provides conditions in which ARGs and MGEs (including novel or life-threatening combinations) can be selected for or evolve, and (4) is where AMR can move spatially and among host species and environmental subsystems (including humans) at spillover points, largely unchecked. AMR will therefore be amplified, reflected by both the nature of the genotypes and the number of anthropogenic AMR components in environmental subsystems. As such, development of integrated surveillance systems is required to aid understanding of and improvements in preventive and control policies.[16] The role of the environment, including land used for food production, in AMR evolution and dissemination remains understudied. AMR in the environment is not purely the result of human actions. AMR is ancient, having been found in

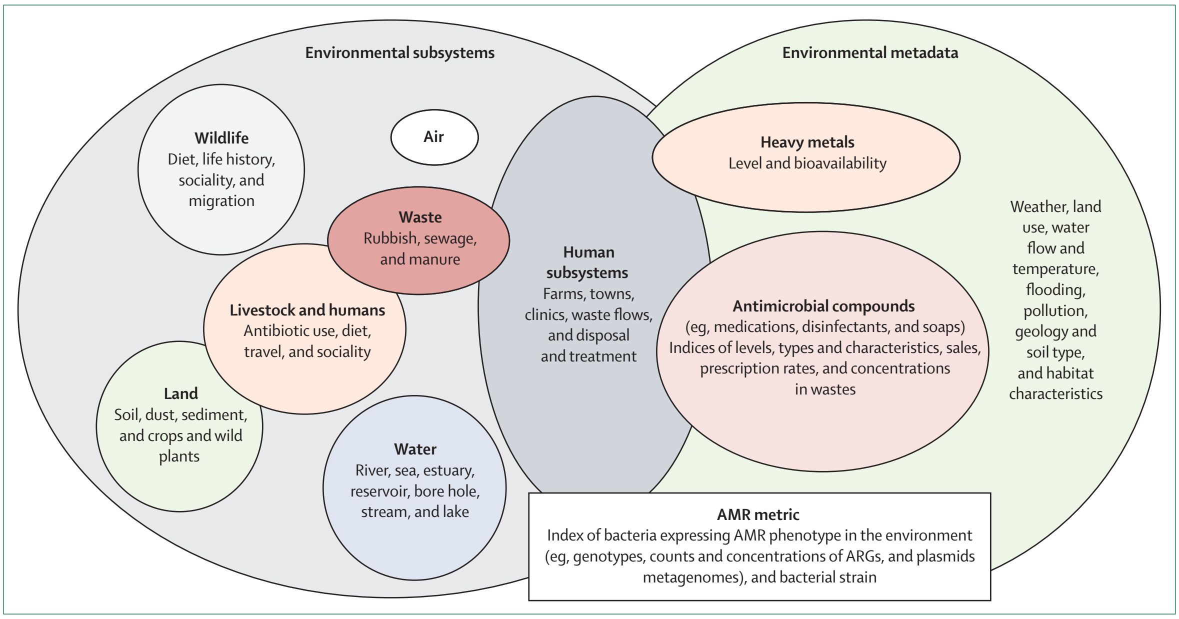

***Figure 3:* Complex, multidimensional data types required to develop systems-thinking, One Health approaches to investigate the role of the environment in AMR evolution, transmission, and dissemination**
Knowledge of the spatial and temporal distribution of the data is particularly valuable. Such datasets will derive from various sources including surveillance schemes, environmental monitoring by regulators, open-source data from academic studies, and statutory reporting by companies. AMR=antimicrobial resistance. ARGs=antimicrobial resistant genes.

permafrost, and resistance mechanisms have probably existed for millions of years as an evolutionary consequence of microbial competition in stressful environments.[17] However, clinical and agricultural use of antibiotics since the 1950s has resulted in increasing levels of ARGs found in the environment (eg, in soils).[18,19] Although there are now many studies showing AMR in wildlife and the natural environment,[20] which can indicate spillover from antibiotic treatment, there is little focus on whether this is important to human or livestock health and if so, how.[21] This knowledge gap is reflected by the lack of prominence of the environment in global and national action plans on AMR control and prevention.[22,23]

Several reasons could explain why the environmental dimensions of AMR are frequently sidelined. First, understanding the development and transmission of anthropogenic resistance involves interactions between the physical environment, social exchanges between all hosts and settings including clinical and, in host communities, the food production chain (pre-farm and post-farm-gate to fork), and human-use and effect patterns (figure 2).[24,25] Such interplays are complex[26] and therefore difficult to study or quantify. Thus, the environmental dimension of AMR presents a classic One Health problem that needs systems-based solutions.[8,13,27,28] Second, differences among disciplines in terminology include definitions of both the terms “environment” and “environmental AMR”,[29] which can spill over into differences across disciplines and sectors in what is considered relevant or high-quality research. Third, in the real world and at field scale, environmental microbiology is disorderly, complex, and hyper-connected in ways that transcend our current taxonomies and disciplines (figure 1). Moreover, it is not easily perceptible to the involved actors (eg, farmers).[25,26] Consequently, observations or experiments (eg, in rivers, farm fields, or wastewater treatment plants) are challenging to replicate compared with laboratory studies that are highly repeatable and tightly controlled.[23] Finally, as we try to bring an ontological framework to environmental AMR,[22,23] it becomes clear that these different elements or actors operate at different levels of biological scale and are not static in space or time.[30,31] For example, here we incorporate concepts of epidemiological or environmental subsystems encompassing the biotic factors (ie, animals and plants including highly mobile species of wildlife, such as migratory waterfowl),[20,30] livestock entering the human food chain,[32] and abiotic sinks (eg, soil and water).[33,34] Incorporating these concepts is important because the literature increasingly confirms that AMR is ubiquitous in wildlife species and other environmental subsystems, such as waterways and soils.[20,35–37] Understanding the interactions between such subsystems is crucial to model and predict intra-subsystem and inter-subsystem transmission of AMR during the evolutionary process, leading to development of further resistance mechanisms (figure 2).[20,26,30] Historically there have been constraints on assessing the role of the environment in AMR, but in this Personal View we argue that new technological methods and theoretical approaches can overcome some of these constraints and address some major unanswered questions.

	Stakeholders	Solutions and opportunities
Accessing data for systems thinking approaches including to complex and large-scale data		
Culture and knowledge around prescribing (eg, patient, livestock producer, pet owner, and arable producer confidentiality) means that fine scale prescribing data are not available	Clinicians and hospitals, veterinary staff and practices, and agronomists and arable producers	Data passed through ethics for clinical trials or research will have already been passed through an anonymisation process and should be regularly provided at sub-national scale. National-level governance, planning, and regulatory and legal frameworks should be developed for AMU including production, sales, and disposal of unused and expired antimicrobials.
Variation in literacy levels means that there is difference in understanding of the appropriate use of antibiotics and the recording of antibiotic use, and in ecological pest management strategies	National governments and other agencies and pharmaceutical companies	Invest in education particularly of girls and women. Pharmaceutical companies could provide key information via videos or audio, use infographics and images, and use digital and other forms of storytelling. Avoid jargon. Recording of AMU can be improved using smart technologies and by providing training to stakeholders.
Variable availability across countries of commercially sensitive sales and environmental effect assessment data	Antibiotic supply chain, regulators, and water companies	Incentivise or create legislation to acquire data particularly from private sector organisations. National-level regulatory and legal frameworks should be developed for AMR, including facilitating data availability.[41]
Recording of over-the-counter antimicrobial compound sales varies globally and regionally	Veterinary practitioners, pharmacists, and regulators	Collect empty antimicrobial packaging via special bins[42] to estimate antibiotic use by patients, farmers, and animal owners, as an alternative or addition to data on prescription or regarding sales.[41]
AMR relevant compounds (chemical and biological) not routinely monitored or recorded for conventional ecotoxicological effects in addition to AMR	Water and waste companies and national environmental protection agencies	Review monitoring requirements and standardised risk assessments to establish international standards for indicators describing AMR development and transmission in environmental and other samples.[41] Increase integration of environmental considerations into National Action Plans on AMR; for example, chemical pollution and waste management programmes, national biodiversity, and climate change planning.
Access to and capacity to analytically mine genomic datasets for AMR determinants that reflect the One Health dimension	Molecular biologists and data scientists	Perform comparative analysis of resistance genotypes allied to the burden of selection in environmental and clinical and agriculture subsystems and systems.
Identifying appropriate environmental and contaminant datasets to collate and provide as evidence in relation to AMR co-selection	Environmental scientists	Need for more studies of the mechanisms driving resistance and co-selection mechanisms in complex environmental media and matrices to support bans. Conduct further research to understand the roles of sublethal disinfectant concentrations, herbicide, and microplastics on AMR emergence.
Integrating diverse data sources		
Locating highly dimensional and complex metadata sets	National governments and regulators	Identify routinely collected data streams including existing EU and global inventories, databases, and observatories that can be fused (eg, US Geological Survey, NORMAN network, and HBM4EU databases).
Mapping complex and long-distance movements of wildlife potentially involved in AMR dispersal	Ecologists	Use tools from movement and migration biology to track dissemination of AMR genes, including global tracking satellites.
Data (eg, wildlife tracking data) collected for other purposes	Geographical information systems experts and ecologists	Specialised studies and datasets need to be commissioned. Use agreed international standards for collecting, storing, and sharing remote-sensing datasets.
Technical challenges of integrating and analysing highly dimensional and complex datasets	Data scientists and national governments	Set up the standards and data quality methods needed to record and analyse the collected data using a multidimensional lens. Invest in data-science innovation and training.
Lack of collection of data (and integration with other AMR datasets) that will further the understanding of social context for antimicrobial compound use and other drivers of behaviour change	Social scientists and practitioners in community public and veterinary health	Develop socially innovative mechanisms for effective engagement and good practice with key stakeholders and communities ensuring effective data collection and transnationally valid outputs. Work with gatekeepers to access hard-to-reach communities to understand contextual behaviours and promote necessary change by raising awareness and helping the community develop their own sustainable solutions.

(Table continues on next page)

For more on the **US Geological Survey** see https://data.usgs.gov/datacatalog/

For more on the **NORMAN network** see https://www.norman-network.com/nds/.

For more on the **HBM4EU dashboard** see https://www.hbm4eu.eu/

A key knowledge gap is the extent to which the release of antibiotics, other antimicrobial chemicals, heavy metals, and their bioavailability, versus ARGs, contribute to the evolution, spread, and persistence of AMR in the environment.[38] Environmental evidence of AMR and potential AMR-drivers needs collating with updateable, plastic systematic and structured data storage mechanisms, to facilitate the resource's expansion with updated or emerging information. By clarifying the relative importance of antimicrobial disposal versus ARGs in wastes, on the development of further resistance, for example, we could establish improved interventions to regulate and control the release of waste and byproducts, such as manure, sewage, and emissions from pharmaceutical manufacturing to reduce environmental AMR and antimicrobial contamination.[39] Given that the movement of pollutants does not respect transnational boundaries,[40] analytical approaches are required that can identify, interrogate, integrate, and interpret diverse and complex datasets (summarised in figure 3) at different spatial and temporal scales.[27]

Challenges in developing systems-thinking approaches to AMR

There are challenges to collating data using systems-thinking One Health approaches (table), and data-science methodologies need to be sufficiently structured and holistic to address these variable aetiologies (figure 3 summarises some of the data required).[23] There is a need to: (1) access complex and large-scale data by knowledge-mapping the data ecosystem, (2) integrate and visualise diverse data sources, (3) understand how to synthesise

	Stakeholders	Solutions and opportunities
(Continued from previous page)		
Interpreting and synthesising AMR data collected using different methods		
Patchy, context-dependent, inconsistent, and incomplete data on AMR distribution in the environment in relation to human activities	Scientists, spatial modellers, and regulators	Metrics for measuring anthropogenic AMR and optimal surveillance strategy to identify key risks and drivers. Use globally agreed data standards and metadata standards.[43] Use of One Health systems approaches to respond to AMR at global, regional, and country levels from all sectors, stakeholders, and institutions.[41]
Integrating evidence from multiple AMR diagnostic methods, which differ in their diagnostic specificities and sensitivities	Veterinary and public health experts	Use clinical algorithms to integrate and interpret genomic data and traditional susceptibility data to locate known resistance genes and identify novel mutations that result in resistance
Incomplete AMR surveillance in animals with most of the reported data relating to scanning surveillance	Regulators and governments	Active surveillance of AMR across companion animal, equine, and food producing animal species.[2] Better understanding of these species-specific subsystems is needed.
Spatial and temporal resolutions of data recording vary	Spatial modellers and regulators	Compare and integrate data from different spatial and temporal resolutions to help harmonise surveillance
Understanding data biases, synthesis of data sources, and data gaps		
Sampling biases; for example, over-representation of data from certain countries, habitats, and species	National governments	Pan-national investment in global science capacity building and AMR, environmental, and other surveillance and monitoring schemes is needed.
Problems with accessing, sharing, and storing data, particularly if commercially sensitive or confidential	Legislators, water, and industry	Widespread agreement on use of FAIR (findable, accessible, interoperable, and reusable) principles to develop technical, legal, and other solutions.[44]
Legislation and enforcement against counterfeit pharmaceuticals are absent in some countries, which results in a poor understanding of AMU	Legislators and regulators	Encourage countries to include data collection and act against counterfeit drugs in National Action Plans for AMR.[21]
Incomplete knowledge about the true AMU by end users; for example, patient or farmer compliance with antibiotic treatment, missing doses, mixing with alcohol, or traditional remedies	Behavioural scientists and pharmaceutical companies	Conduct studies to explore reasons for non-compliance of patients, veterinary practitioners, and farmers with prescription advice. Implementation of behavioural change with patients, farmers, and veterinary practitioners (ie, only use compounds when necessary and finish the course of antimicrobials).
Interpreting outputs for business, policy makers, and decision makers		
Complex, multidimensional data, and the analyses of such data are difficult to interpret for the purposes of policy making and decision making	Data scientists and civil servants	Use sign-posting tools; for example, data visualisations and dashboards. Use Monte Carlo simulations to provide measures of certainty on outcomes that could be easily coded akin to the traffic light labelling for food.
Lack of understanding of the effects of cost–benefit analyses that are important to key stakeholders	Social scientists and scientists	Develop national and global surveillance projects to ensure that environmental data and metrics are incorporated into a theory of change that is co-developed with stakeholders including communities, industries, and clinicians.
Lack of understanding by decision makers as to the relative costs, benefits, risks, and uncertainties of the current status and future mitigation options	National government and international health and environmental organisations	Generate fully costed options for mitigation or biosafety control measures that reduce routes of AMR transmission on a planetary scale (ie, not only for AMR reduction, but including other environmental and social benefits).
Disconnect between evidence and policy; for example, the traditional policy approach involves stakeholder consultation after policy options have been outlined	Regulators, government, and community stakeholders	Greater use of the One Health co-design approach, which offers an opportunity to direct policy decisions through a collaborative approach with key stakeholders[25] (eg, in a national action framework). Integrate AMR in national development planning and budgeting, and national chemical pollution and waste management programmes.[41]

Potential solutions to and opportunities provided by these five challenges were proposed by workshop attendees and according to recommendations from the United Nations Environment Programme.[41] AMR=antimicrobial resistance. AMU=antimicrobial usage.

Table: **Mapping the challenges and opportunities facing stakeholders in collating data using systems-thinking, One Health approaches to AMR**

AMR data collected using different quantitative field and laboratory methods in addition to contextual qualitative approaches explaining behaviour including decision making, (4) develop methods to describe the likelihood and uncertainty (including biases) in synthesised relationships and data gaps, and (5) clearly and fairly interpret and present data to end users (eg, policy makers), whilst explaining the knowledge-gain from new approaches using measurable indicators via project evaluations (table).

Accessing data for systems-thinking including complex and large-scale data

Antimicrobial use and subsequent release in waste, for example, varies at all spatial resolutions within and among countries.[3,45,46] Across the world there are cultural differences in knowledge of prescribing and ready availability of some crucially important antibiotics.[25,47] In agriculture, some countries are better at using narrow spectrum antibiotics, whereas in others, farmers and veterinary practitioners believe that multiple types of broad-range antibiotics have a greater effect.[48,49] Also, there are big differences in the information recorded and collated within public and veterinary public-health systems in labelling and regulating antibiotic use,[49] and in the use of counterfeit pharmaceutical products[50] and enforcement against these.[25,47] Capturing metadata describing policy, cultural, and practice context within big datasets will require collaboration with social scientists,[51] and using key local champions to mobilise local livestock holders, policy makers, and veterinary practitioners among others.[52] Although difficult, it is not impossible (with collaboration from stakeholders in the supply chain) to record whether each country has legislation mandating the recording of over-the-counter antimicrobial sales and information on which antimicrobial compounds are sold.[49] Unfortunately, whether any legislation is complied with and enforced would be more challenging to record at scale not only because compliance might be monitored differently in different regions,[49] but also because it is recorded as textual data, thus requiring interrogation of case studies, natural language processing frameworks, and links to, for example, the European Legislation Identifier.[53] In addition, much of the necessary data will come from public or private sources and might be personally sensitive or market-sensitive, with data providers being potentially unwilling to share data at appropriate resolutions.[54] Secure methods for data sharing are therefore necessary, and should use the highest levels of research integrity and be legally compliant; tools for integrating specific sources of sensitive information have recently been developed for both human clinical and animal health information.[55,56] Lack of access to some types of sensitive data might be circumvented by applying systems approaches in which causal chains are illustrated and flows of, for example, antimicrobials can be modelled in sensitivity analyses within subsystems and the effects on the greater systems could be predicted.

Integrating diverse data sources

Quantifying antimicrobial drug use would only provide partial insight into the potential for anthropogenic activity to select for AMR.[57] There is a need to integrate diverse data sources to study AMR development. For example, clear evidence from both laboratory and field-level studies shows that AMR can be driven by co-selection by other chemicals released into the environment including biocides used to disinfect hospitals, homes, and farmyards, and in cosmetic products and industrial processes.[23,38,58] Agricultural run-off, mining, municipal wastewater, and industrial waste are point-sources of heavy metal pollutants that can bioaccumulate and persist in the environment.[38] Co-selecting for resistance, these complex cocktails of chemicals in human and livestock waste[43] are released into the environment. However, accessing and integrating the different datasets so that they can be used to test for correlations between land use (or a specific anthropogenic activity—eg, smelting) and AMR will be challenging logistically and politically.[52,59–61]

That said, there has been an explosion in the production of, and often open access to, remote-sensing datasets. Improved availability of more traditional ecological and environmental monitoring datasets (eg, water quality, land-use cover, and wildlife migration) is needed to aid identification of pertinent variables.[62] Such metadata can now potentially be spatially and temporally linked to burgeoning numbers of studies showing AMR in a variety of environmental subsystems and systems around the world. There is an additional challenge to synthesising these types of quantitative data describing where and in whom AMR is identified, with qualitative contextual data detailing relevant behavioural, cultural, and policy changes.[51] The contextual data could explain systematic changes in quantitative data (eg, a policy change driving greater identification of AMR), and could potentially be applied within the systems-based framework, as a sensitivity analysis exploring why AMR changes happen.

Interpreting and synthesising AMR data collected using different methods

When applying data-science approaches, such as clinical settings, a medley of AMR metrics are recorded for environmental subsystems. Each metric has advantages and disadvantages, depending on the scientific questions and available field technology. Multiple genotypic approaches are increasingly prevalent in the literature that aim to deliver rapid AMR results by probing for the presence of specific genetic sequences known to cause phenotypic resistance. Genomic approaches can distinguish large numbers of ARGs, gene cassettes, and MGEs; however, this relies on identifying such sequences from previous studies. Genetic approaches will not pinpoint novel mutations that are particularly likely to arise in environmental subsystems, including wildlife.[20] Classical AMR susceptibility testing involves culturing bacterial isolates in antibiotic-infused media, which although time consuming, allows identification of phenotypically resistant bacteria and aids in the identification of those genes or gene cassettes that have not previously been identified as conferring resistance. Therefore, there are benefits to using the large and rapidly produced AMR datasets arising from gene-centric studies, particularly for large-scale surveillance[63,64] to identify sites for further on-the-ground investigation. However, analysis of phenotypic resistance will be needed to fully diagnose high-risk hotspots of novel AMR where policy, scientific, or process changes are required.

The various AMR diagnostic methods described have their challenges, because each method used in each setting will have different diagnostic specificities and sensitivities. The results of multiple tests will therefore need careful evaluation and interpretation so that their combined results are appropriately synthesised. To achieve this, the public and veterinary public-health fields already develop and use clinical algorithms, which could potentially be modified to integrate AMR tests from environmental subsystems.

Understanding data biases, synthesis of data sources, and data gaps

Additional to the technological challenges of analysing highly dimensional and complex datasets, systems-based approaches will require an analytical mechanism to understand (or even adjust for) potential biases in data reporting associated with some host species and environmental subsystems. For example, humans, some livestock species, and some environmental subsystems are heavily sampled and others are rarely or never sampled.[26] Sampling biases can occur due to selection differences resulting from: ease of sampling (illustrating the aforementioned need for different sampling methods); difficulties associated with identifying appropriate data; data storage and sharing issues resulting from different sampling methods (small *vs* big data such as informatics data); funding for research focusing on specific hosts, environments, and geographies, which do not always coincide with high-risk hotspots or reservoirs[52] (eg, funding availability in developed *vs* developing countries,[49] and human *vs* environmental research funding pots);[29,37] and due to data confidentiality issues (eg, patient, client, or industry-held data).[25,54] Use of the FAIR (findable, accessible, interoperable, and reusable) principles should reduce such issues;[44] however, within the next steps for studying AMR in the environment, their careful consideration is needed.

As information from data sources is combined and synthesised into understanding, it is useful to develop mechanisms to quantify the certainty around the synthesised relationships. An appropriate structure could be similar to disease and biological risk assessment,[65,66] which describes the likelihood and uncertainty of understanding for and in this case each combination of bacterial pathogen, type of AMR resistance, host, and environmental subsystem. A data gap is identified when there is a negligible or low likelihood of there being evidence of a pathogen, AMR type, host, or environmental subsystem relationship, with low uncertainty.

Interpreting outputs for business, policy makers, and decision makers

To fulfil the policy and business needs of stakeholders, these integrated datasets can then be made accessible to end users by providing simple sign-posting tools to make decisions; for example, data visualisations and dashboards that can then be used as living review tools and mechanisms to provide the evidence base to change policy.[67] The challenge is interpreting the observed patterns because more data that is better presented will not necessarily provide a different or right conclusion. Also, it is important that those interpreting the data have sufficient experience to appropriately understand outputs.[68] However, by effectively integrating information in a meaningful and secure manner and with appropriate interpretation, users will be able to best understand which elements of the AMR system require further investigation, and which are likely contributing to its effects.

To understand the effects and enable modifications to current antimicrobial practices, measurable indicators of changes in resistance metrics are necessary to create leverage for business and policy and decision makers. We need to be able to show that an intervention results in a positive and measurable change to an environmental subsystem or ideally full system, an improved cost–benefit outcome for the environment, or has increased acceptability to stakeholders.[69] Such outcomes of interventions would need to be built into the theory of change in the project evaluation. The theory of change, a methodology used by business and policy and decision makers to promote social change, links and metricises inputs in a system to activities that need to occur to outputs from the process and outcomes that are recognisable and useful to the business and policy and decision makers. A conceptual framework for developing a One Health theory of change that includes the environment has recently been published by the One Health High Level Expert Panel.[70]

Modelling approaches

Our understanding of AMR dispersal is currently restricted to a small (ie, subsystem) scale; for example, in an individual's gut, a slurry tank,[71] a hospital, or a wastewater treatment plant. One key challenge for applying One Health approaches is to be able to model AMR in the environment at a much larger and systems-thinking scale, which requires more data and greater computational processes. A modelling approach will enable us to better understand AMR, control it, and react to any outbreaks. It is particularly difficult to develop predictive models of AMR subsystems and systems, as at present there is a theoretical metric but no literal method for quantifying anthropogenic AMR.[72] As a proxy, there could be utility in tracking the use of antimicrobials in humans in hospitals as sources and then quantifying antimicrobial movements via ecosystems (eg, urban, peri-urban, and rural ecosystems).

There are common approaches within systems-thinking[73] that could be used to understand AMR flow around the environment, explore characteristics of transmission drivers, then identify and fill knowledge gaps. These approaches include using Bayesian networks, dynamic modelling, agent-based modelling, and social network analysis. These approaches help to interpret multifarious data, particularly when coupled with approaches such as concept mapping, stock and flow diagrams, and causal inference.[74] The power of modelling methods is to also extrapolate existing knowledge to estimate what happens in similar species and environments. Therefore, if we could better understand the drivers of AMR emergence and dissemination in a well studied species, such as dogs, we could, based on our knowledge of their diet, behaviour, and distribution, use phylogenetically based models[75] to make statistical predictions about whether a closely related species (eg, grey wolf) foraging on human waste in urban areas could be concerning.

Phylodynamic studies are also an appropriate approach to examine the transmission of resistance. Interdisciplinary collaborations in modelling studies facilitate interpretations of datasets, so that routes of transmission and geographical distribution of resistance can be best understood to guide optimum sampling points for surveillance.[64] Moreover, systems-based models have the power to test counterfactual scenarios or large-scale policy changes that would be too difficult, costly, or unethical to assess empirically.[71] Finally, although modelling studies can provide a better understanding of the quantity rather than the presence of resistance, there is a need to be cognisant that all models are imperfect and provide a simplified version of their quarry. When used to predict future scenarios and understand knowledge gaps, modelling studies need cautious interpretation.

Benefits of applying holistic, systems-thinking approaches to tackling AMR

While there are challenges in applying holistic, systems-thinking approaches to understanding AMR evolution and dissemination in the environment, there are potential big benefits and opportunities (table). By way of illustration, WHO and other national and international action plans for AMR recommend reducing the release of antimicrobial medications into the environment from three sources: waste from livestock operations, waste from human sewage, and waste from pharmaceutical manufacturing. The overall goal is to decrease the amount of environmental contamination.[26,39] A systems-thinking approach would break this environmental contamination down into its component parts, including feedback loops, and identify potential control and crucial control points to prioritise interventions. Potential intervention points could include either pre-release of waste from the hospital, wastewater treatment plants, or farms (eg, decreasing consumption of medications or use of alternatives, such as green prescribing[39] or reducing or recapturing chemical drivers entering the waste stream), or post-release in terms of clean-up in geographical areas.[23] However, these interventions would involve high costs and major changes to policy, and industrial and farming practices that could be unpalatable to stakeholders, unless incentives were available. Using holistic and systems-thinking approaches that integrate multiple data sources offers the potential to understand AMR pathways and drivers in the environment, and we can explore preventive and treatment methods so that the most cost-effective mitigation strategies can be shared with decision makers. By looking at the problem at a subsystem and then greater systems level, costs will be calculable and shared across the whole system, creating savings in overall intervention costs.

Systems-based approaches applied within a One Health framework could be used to create a predictive tool to provide evidence for advocacy, influencing decision making around AMR. Such a tool would enable researchers to help policy makers take informed decisions on a range of issues. First, where gaps in evidence exist, decisions can be made on where to undertake surveillance and thus allocate funding. Second, decisions can be made on the optimal surveillance strategy to identify key risks and crucial control points, such as at interfaces between humans and potentially contaminated environmental subsystems with high potential for the evolution of novel ARGs. Third, informed decisions on the relative weight of evidence supporting specific surveillance strategies and appropriate sampling methods for surveillance (eg, frequency of sampling, the pooling of samples, or how resistance is identified). Last, such a tool could be helpful in identifying mitigation or biosafety control measures to cut off routes of transmission (eg, movement of manure from antibiotic treated animals to fields adjacent to waterways and habitations).

Conclusion

Systems-based data-science approaches are already being used by some public health organisations to monitor or even predict clinical risk.[76] Here, we argue that these approaches are essential to help assess the role of the environment, in its broadest sense, as a key element in the AMR system, which would also prove a useful blueprint for wider use in other complex systems requiring an evidence base for risk assessments. There are some challenges and caveats to integrating, modelling, and interpreting diverse datasets. As discussed, one major issue is data biases at every spatial and biological level. Also, the AMR system is complex with interconnected processes, causal loops, and emerging properties. However, the development of such a multi-domain data resource will provide a mechanism to undertake gap analysis to identify potential new research avenues. Importantly, the application of systems-based data-science approaches within a One Health framework has the potential to assess AMR at both a subsystem and a system level, providing evidence for researchers, regulators, and policy makers to make decisions on the basis of evidence regarding interventions to slow the emergence and spread of AMR globally. Such decisions will have implications for societal capacity to meet sustainable development goals in terms of equal access to health care, sanitation, food security, healthy ecosystems, globalisation, and economic growth.

Contributors

Contributors to the ideas developed in this manuscript included 16 participants at a workshop on global AMR distribution and transmission in the environment held at the University of Liverpool on July 22–23, 2019. All authors contributed to the conceptualisation of the paper. KEA and KMM acquired funding for the study and were responsible for writing the manuscript. KEA, KMM, GL, SF, BJM, and DJS contributed to writing the draft manuscript and revising the text. All authors contributed to the review and editing of the manuscript.

Declaration of interests

The authors declare no competing interests.

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